PATTERN OF COAGULATION PROFILE IN PATIENTS WITH TRAUMA

Dissertation submitted to

THE TAMILNADU Dr. M.G.R MEDICAL UNIVERSITY
CHENNAI – 600032

In partial fulfillment of the requirement for the degree of
Doctor Of Medicine in Physiology (Branch V)
M.D. (Physiology)
APRIL 2016

DEPARTMENT OF PHYSIOLOGY

CHENNAI MEDICAL COLLEGE HOSPITAL & RESEARCH CENTRE

(Under The Tamilnadu Dr.M.G.R Medical University)

Irungalur, Trichy – 621 105.

CERTIFICATE

This is to certify that this dissertation entitled **"PATTERN OF COAGULATION PROFILE IN PATIENTS WITH TRAUMA"** *is submitted to the Tamil Nadu Dr. M.G.R Medical University, Chennai in the partial fulfilment of regulations for the medical award of M.D degree in Physiology in the examination held during APRIL 2016.*

This dissertation is a record of fresh work done by **Dr.B.AANANTHA LAKSHMI** *during her course of study (2013- 2016). This work was carried out by the candidate herself under my supervision.*

DEAN

Dr.P.G.SANKARANARAYANAN., M.D

GUIDE

Dr.P.RAJENDRAN.,B.Sc, M.D,(Phy)

Place : Irungalur , Trichy

Date :

DECLARATION

I ***Dr. B. Aanantha Lakshmi*** *solemnly declare that the dissertation entitled* ***"PATTERN OF COAGULATION PROFILE IN PATIENTS WITH TRAUMA"*** *was done by me at Chennai Medical College Hospital & Research Centre, Irungalur, Trichy during the period from December 2013 to December 2014 under the guidance and supervision of* ***Dr.P.Rajendran,B.Sc.,M.D.(Phy),*** *Professor and Head of the Department of Physiology, Chennai Medical College Hospital & Research Centre, Irungalur, Trichy.*

This dissertation is submitted to The Tamilnadu Dr.M.G.R.Medical University towards the partial fulfilment of the requirement for the award of M.D. Degree (Branch - V) in Physiology.

I have not submitted this dissertation on any previous occasion to any University for the award of any degree.

Place:

Date:

Dr.B.AANANTHA LAKSHMI

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Pattern of coagulation profile in patients with trauma.

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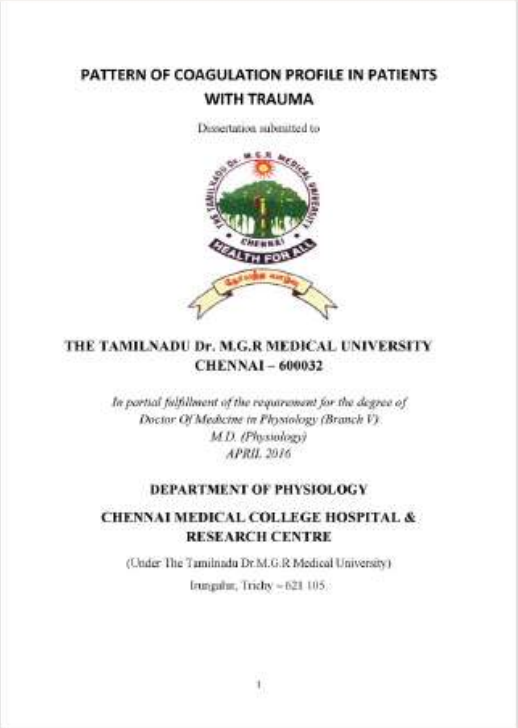

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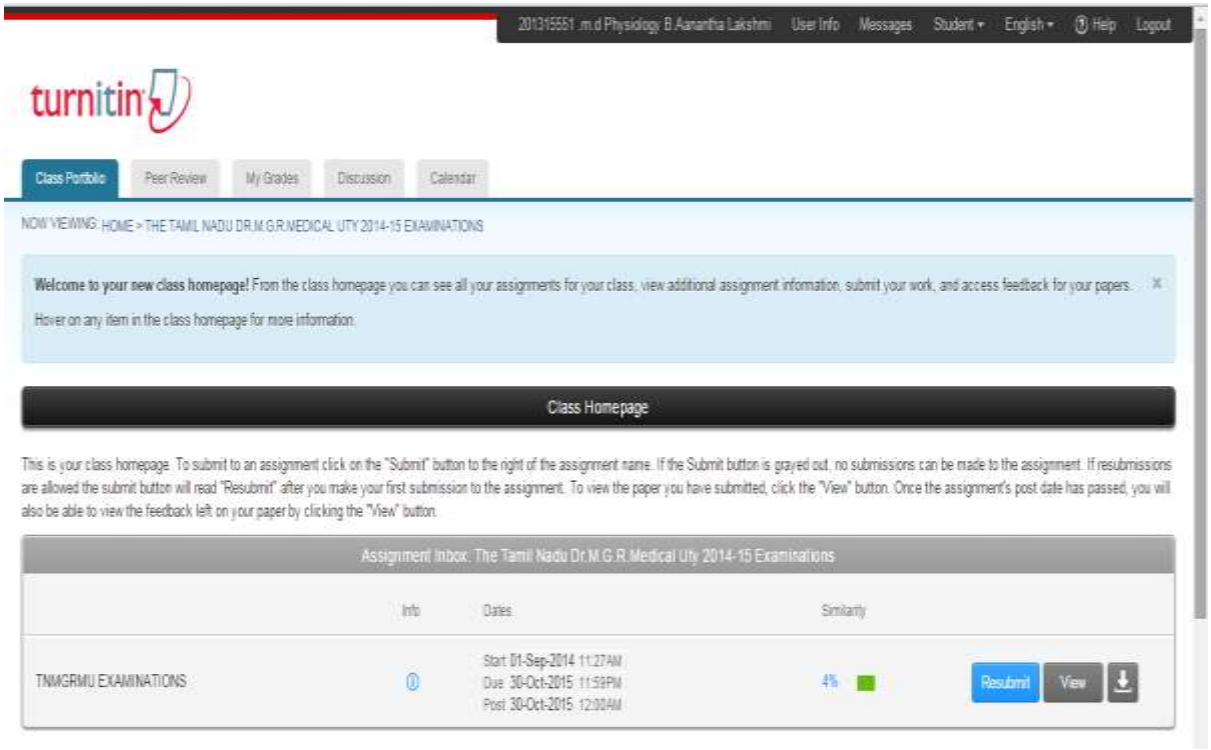
ORGINALITY REPORT



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Last and most importantly I am thankful to all the patients enrolled in this study for extending their valuable co-operation for this study.

(Dr. B. AANANTHA LAKSHMI)

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ABBREVATIONS USED

- PT - Prothrombin Time
- aPTT - activated Partial Tissue Thromboplastin Time
- TxA_2 - Thromboxane A_2
- PGI_2 - Prostaglandin I_2
- PF - Platelet Factor
- TFPI - Tissue factor pathway inhibitor
- t-PA - Tissue plasminogen activator
- CBC - Complete Blood Count
- INR - Internationalised Normalised Ratio
- FDP - Fibrinogen Degradation Product
- FFP - Fresh Frozen Plasma
- PRBC - Packed Red Blood Cells
- TIC - Trauma Induced Coagulopathy
- TBI - Traumatic Brain Injury
- ISS - Injury Severity Score
- aPC - activated Protein C
- TICU LOS - Trauma Intensive Care Unit Length Of Stay
- ATC - Acute Traumatic Coagulopathy
- RTS - Revised Trauma Score
- ARI - Acute Renal Injury
- AIS - Abbreviated Injury Scale

- CT - Computerised Tomography
- DIC - Disseminated Intravascular Coagulopathy
- IVF - Intravenous fluid
- MOD - Multi Organ Dysfunction
- PAI – 1 - Plasminogen Activator Inhibitor - 1
- HCO_3^- - Bicarbonate
- PO_2 - Partial pressure of oxygen
- PCO_2 - Partial pressure of Carbon-di- oxide
- r -TEG - Rotational Thromboelastography
- TEG - Thromboelastography

ABSTRACT

Trauma is the fifth leading cause of death in individuals between age 5 and 45 years worldwide. It will become the second leading cause by 2020. Significant blood loss can occur due to traumatic coagulopathy caused by trauma, called "Acute Traumatic Coagulopathy". This has been scantily described in the literature. Hence this study is aimed to study the effect of trauma on different parameters of coagulation profile and markers of fibrinolysis. 60 trauma patients between age 20 and 60 years were included. The incidence of coagulopathy was found to be 34% and overall mortality rate was 10.3 %. Association of variables like Tissue hypoperfusion, Severity of Injury, etc. with coagulopathy was proved to be statistically significant ($p < 0.05$). Association of the abovesaid variables with mortality was also studied and some were found to be significant. Those which were significant in univariate analysis were taken for multiple logistic regression analysis. Patients presenting with an established coagulopathy were likely to have poor outcomes, and hence must be identified as soon as possible and treated aggressively.

Key words: Trauma, coagulopathy, Coagulation profile, Tissue hypoperfusion, Base deficit,

INTRODUCTION

Trauma is the fifth leading cause of death in individuals between age 5 and 45 years worldwide. It will become the second leading cause by 2020.[1] Significant blood loss can occur due to traumatic coagulopathy caused by trauma.[2-3] This entity called "Acute Traumatic Coagulopathy" has been scantily described in the literature.

Traumatic coagulopathy of acute onset has been elucidated as an acquired disorder of blood coagulation system that happens due to loss or diminished function of proteases enzymes of coagulation system and platelets. Severe trauma may lead to immense bleeding with stimulation of coagulation factors. This further cause subsequent exhaustion of the coagulation factors.[4] The residual procoagulant potential also gets weakened by the administration of colloids and crystalloids. Colloids can directly disturb fibrin polymerization.[5]

The achievement of hemostasis can also be disturbed by many factors like hypothermia, increased fibrinolysis, acidosis, and alterations in the electrolyte values. Among all these factors, first three factors straight away affect fibrin polymerization and metabolism.[6-7] There is only partial increase in synthesis of fibrinogen during blood loss. This increase cannot be reimbursed due to concurrently occurring increased fibrinogen breakdown.[8-9]

The incidence of traumatic coagulopathy was 71% as already been reported by previous studies[10]

Studies which are done recently have concluded that approximately 25% of patients with trauma present to the hospital with a coagulopathy when they seek admission which affects their overall outcome.[4]

Coagulopathy remains an independent predictor of death among various predictors like severity of injury and degree of shock and this has been already proven by previous studies.[11]

The Prothrombin time is a test to assess the decreased levels of factor VII and hence it may be mildly prolonged in trauma. Isolated elevations of the Prothrombin time reveals factor VII deficiency alone and are not indicative of severe coagulation defects. Prolonged aPTT in trauma indicates multiple and severe defects. Increased aPTTs over 1.8 times than controls has been associated with bleeding in several studies.[12-13]

Coagulopathy is not only constrained to mortality but also related with unfortunate clinical outcome like acute renal injury, increased blood transfusion and prolonged stay in hospitals.[14-15]

In view of this, the present study is planned to study the effect of trauma on coagulation profile. Thus the basic coagulation tests like Bleeding Time, Clotting Time, Platelet count, Prothrombin Time (PT), Activated Partial Thromboplastin Time (aPTT) and other parameters like Fibrin, Fibrin Degradation Products, D- Dimer as a marker of fibrinolysis have been included in the study. Base deficit is also included as a marker of tissue hypoperfusion.

This study is also planned to study the outcome variables related to morbidity like length of stay either in ICU or in the general ward, complications like acute renal injury and mortality of the trauma patients and their association with the coagulation profile.

AIM AND OBJECTIVES

AIM

To study the effect of trauma on different parameters of coagulation profile and markers of fibrinolysis.

OBJECTIVES

- To find out the prevalence of coagulopathy in trauma patients and to study its association with severity of injury.
- To study the relationship between tissue hypoperfusion and coagulopathy.
- To study the association between blood transfusion and coagulation defects.
- To determine the association between coagulopathy, tissue hypoperfusion, renal injury and clinical outcome variables like morbidity and mortality.
- To predict the role of PT, aPTT on mortality.
- To find the association of severity of injury with tissue hypoperfusion, lactate level and renal injury.
- To determine the association of Acute Renal Dysfunction and coagulopathy.

REVIEW OF LITERATURE

NORMAL COAGULATION PROCESS

Haemostasis

Haemostasis can be defined as stoppage of bleeding**.** Whenever there is injury to the blood vessel, the first and immediate event is vasoconstriction. This slackens the flow of blood to the affected area.

Stable closure of the vessel by constriction and contact stickiness occurs only in the capillaries; however the stoppage of bleeding ultimately is dependent upon two other processes.

(1) Platelet plug formation and

(2) Coagulation (clotting) of blood.

The blood platelets circulating in blood are involved in both processes.

Platelet Plug formation

The participation of platelets in haemostasis requires their adhesion to a surface of the endothelium. Platelets have a tendency for adhering to surfaces, but they do not stick to the normal endothelial lining of the blood vessels. Whenever blood vessel is injured, the endothelium gets disrupted. This causes exposure of the collagen beneath the endothelium.

Platelets stick to the collagen, by means of **von Willebrand factor (vWF).** This is a plasma protein which is stashed by endothelial cells and platelets. This factor

binds with collagen which gets exposed due to tissue injury. This complex (vWF with collagen) undergoes conformational change, and attains the ability to adhere with platelets; thus vWF forms a link between the injured vessel and the platelets.

Adhesion of platelets to endothelium stimulates the platelets to discharge the contents stored in their secretory vesicles. This includes a variety of chemicals like Adenosine diphosphate (ADP), Thromboxane A_2 and Serotonin. These chemicals induce multiple changes in the platelets like change in metabolism, shape, and surface proteins. This process termed **platelet activation.** Some of these changes cause new platelets to stick on to the old platelets in circulation. This phenomenon is termed as **platelet aggregation** that in turn leads a **platelet plug** inside the vessel.

Adhesion of the platelets rapidly induces them to synthesize **Thromboxane A_2** from arachidonic acid which is a content of the plasma membrane of a platelet. Thromboxane A_2 stimulates platelet aggregation and also helps the platelets to secrete the contents of their secretory-vesicle. This is depicted in Figure 1.

Fibrinogen, a plasma protein also shows a crucial part in the platelet aggregation produced by the factors described above. It forms a link between aggregating platelets. Platelet activation exposes the fibrinogen receptor situated on the platelet plasma membrane.

The platelet plug can entirely seal trivial breaks in wall of blood vessel. Its effectiveness is further enhanced by another property of platelets known as contraction. Platelets contain a very high concentration of actin and myosin, which are activated to contract in aggregated platelets. This causes a compression and thereby strengthens the platelet plug. (When they occur in a test tube, this contraction and

compression are termed as “clot retraction”) While the platelet plug is being built up, the severed vessel undergoes vasoconstriction, thereby decreasing the blood flow to the severed area. This step is mediated by Thromboxane A_2 and by several factors secreted from the secretory vesicles of platelets.

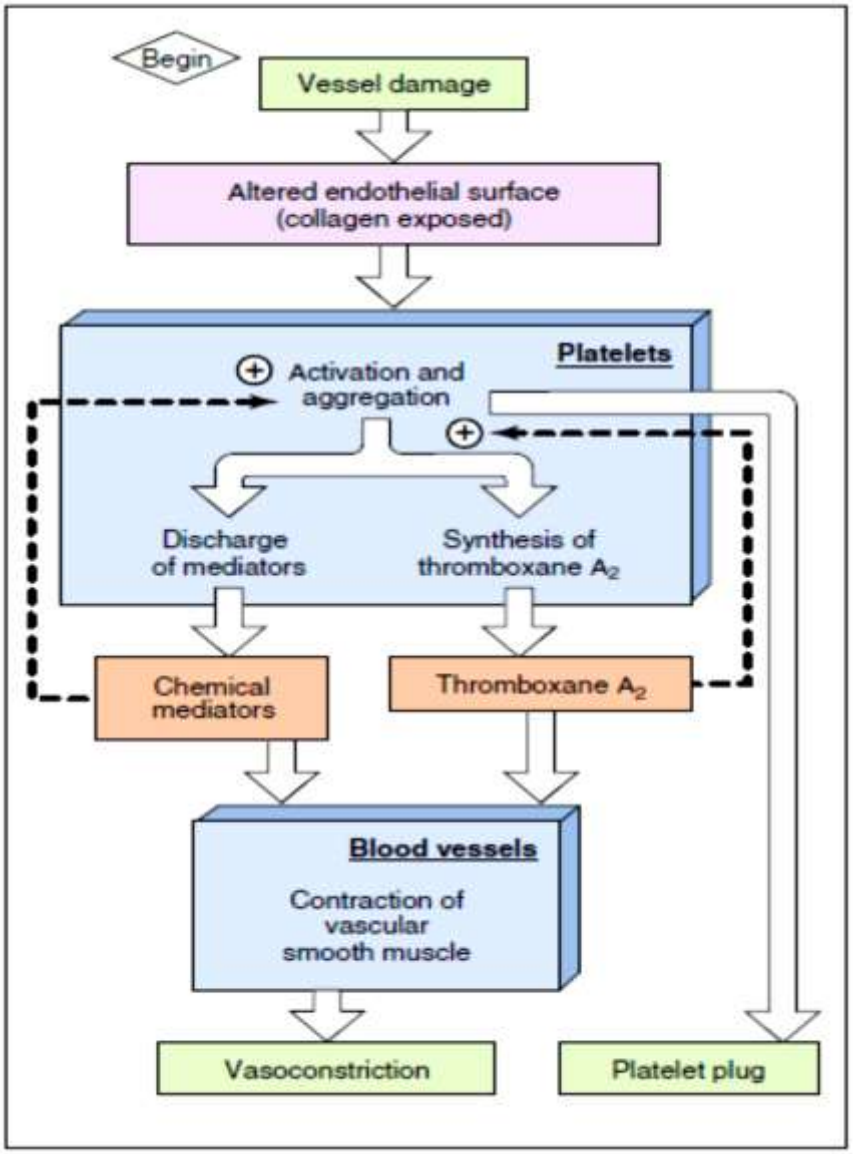


Figure 1 – Steps of Haemostasis

Once started, the platelet plug does not expand continuously, spreading away from the severed endothelium along intact endothelium in both directions. One important reason for this is the synthesis of **prostacyclin** (also termed prostaglandin I_2, (**PGI_2**)). This inhibits platelet aggregation. (Figure 2).

Normal endothelium also releases a potent vasodilator called **nitric oxide,** which also inhibits adhesion, activation, and aggregation of platelets.

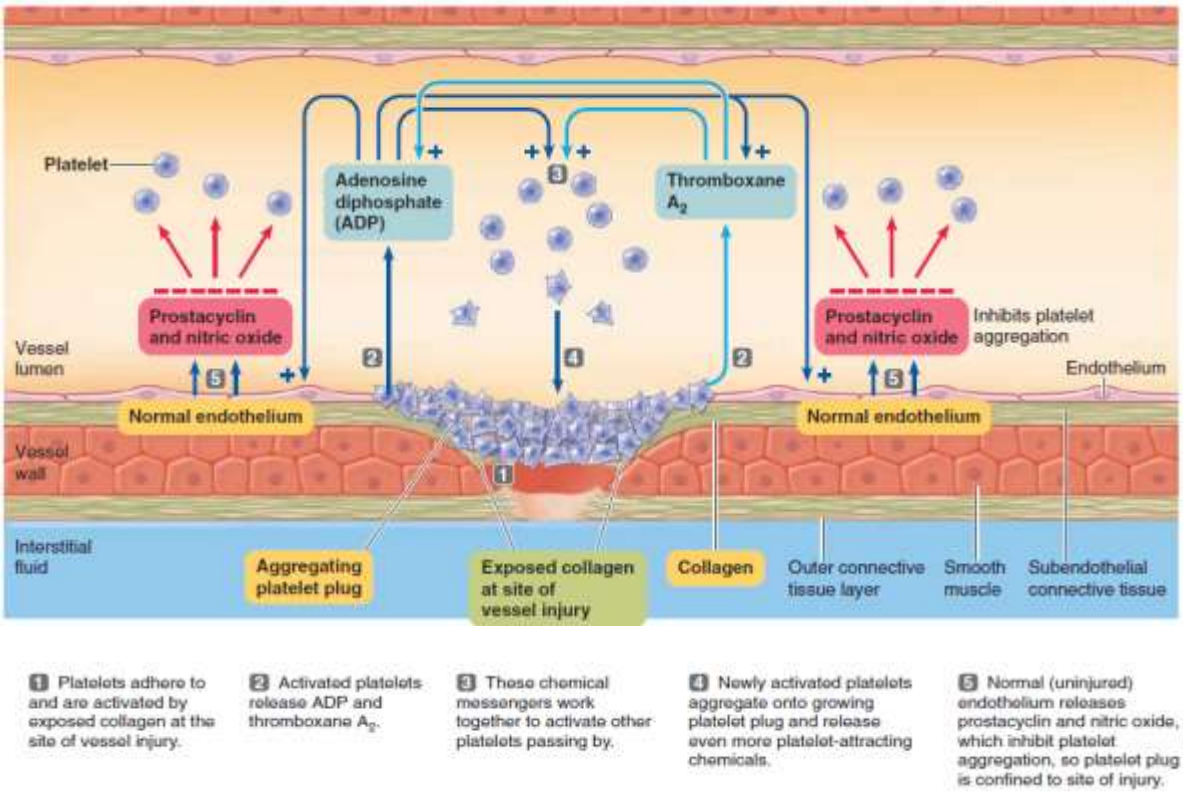


Figure 2 –Platelet Plug formation

Coagulation

The process by which blood gets converted into a solid gel like material is coagulation or clotting of blood**.** The main component of this clot is **fibrin** which is a protein polymer**.**

Coagulation supports and reinforces the formation of platelet plug and helps to strengthen the solidified blood. The contact of platelet plug with the endothelium initiates a locally occurring sequence, or "cascade" of activation of various chemicals.

Plasma protein which is in inactive form, or "factor," is activated to an enzyme which causes proteolysis during each step of coagulation. Thus formed enzyme, catalyses the generation of the next enzyme in the sequence.

The **Prothrombin** is converted to **thrombin** which acts as an enzyme**.** Thrombin catalyses the conversion of **fibrinogen to fibrin.**

Thus formed fibrin is a slack meshwork of interweaving strands. This is quickly become stable and fortified by cross-linkages formed by covalent bonds. This cross – linkage is catalysed by fibrin stabilising factor (Factor XIII) . This factor XIII is activated to factor XIIIa by thrombin. Figure 3 depicts the formation of fibrin clot.

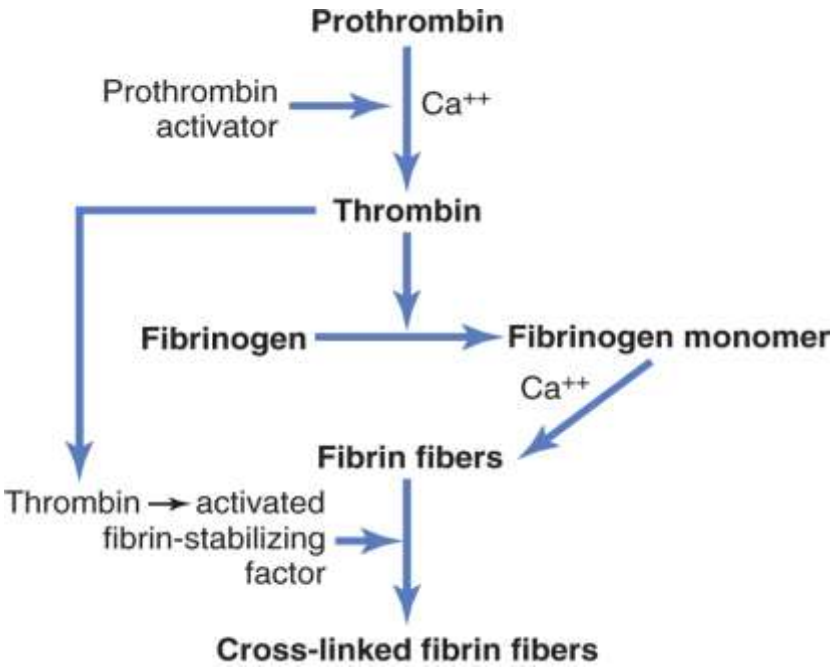


Figure 3 : Formation of fibrin clot

In the process of clotting, many red blood cells and other cells like WBC, platelets etc. are entrapped in the meshwork of fibrin, but the crucial element of blood clot is fibrin. Thus blood coagulation may take place in the absence of any of the cellular components mentioned above except platelets.

The activation of platelets exposes a specific receptor that binds with several clotting factors. This makes the reactions to take place. The activated platelets also release **platelet factor (PF)** which functions as a cofactor in various steps. Calcium present in the plasma is required at various steps involved in coagulation process.

Coagulation cascade

It consists of two seemingly parallel pathways that merge at the step before the prothrombin thrombin reaction. Under physiological conditions, however, the two pathways are not parallel but are actually brought into play *sequentially*, the link between them being thrombin.

The pathways are

(1) **Intrinsic pathway (**everything necessary for it is with***in*** the blood vessel)

(2) **Extrinsic pathway (**blood comes in contact with ***extrinsic*** environment

(i.e) tissue fluid, glass etc.)

Intrinsic pathway

The first factor in the intrinsic pathway is called factor XII. When it contacts certain types of surfaces, including the collagen fibres underlying damaged endothelium, it becomes activated. The activation is a complex process that requires

the participation of several other plasma proteins like Prekallikerin, High Molecular weight Kininogen which are shown in Figure 4.

Factor XIIa then catalyses the formation of factor XIa. This activates factor IX to factor IXa. This last factor IXa helps in the activation of factor X to factor Xa. Factor Xa acts as an enzyme in the conversion of prothrombin to thrombin. Another plasma protein—factor VIIIa—serves as a cofactor in the activation of factor X. [16]

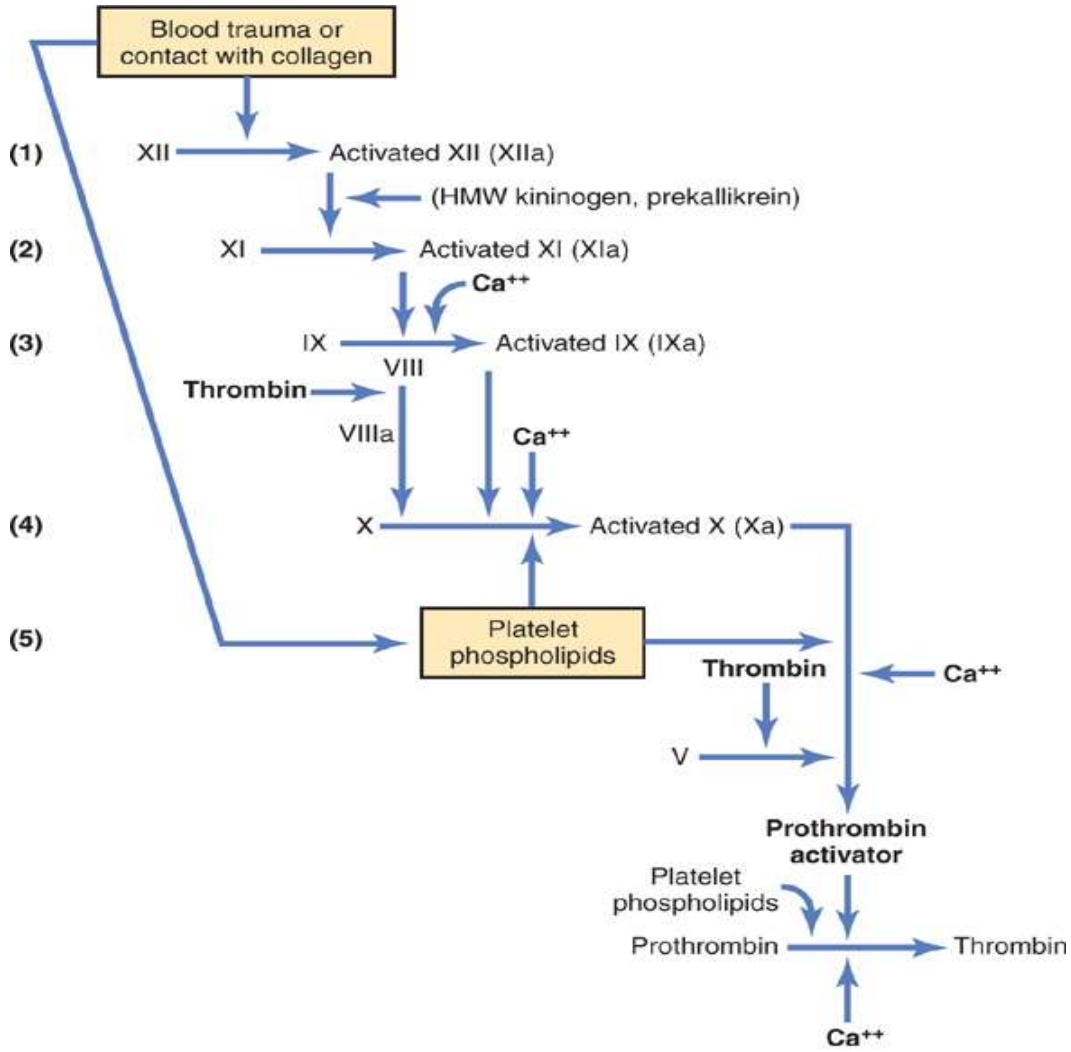


Figure 4 : Intrinsic Pathway of coagulation[17]

Extrinsic pathway

This pathway commences with **tissue factor,** which is found on the outer surface of cell membrane of fibroblasts and other cells in the blood vessel wall beneath the endothelial layer.

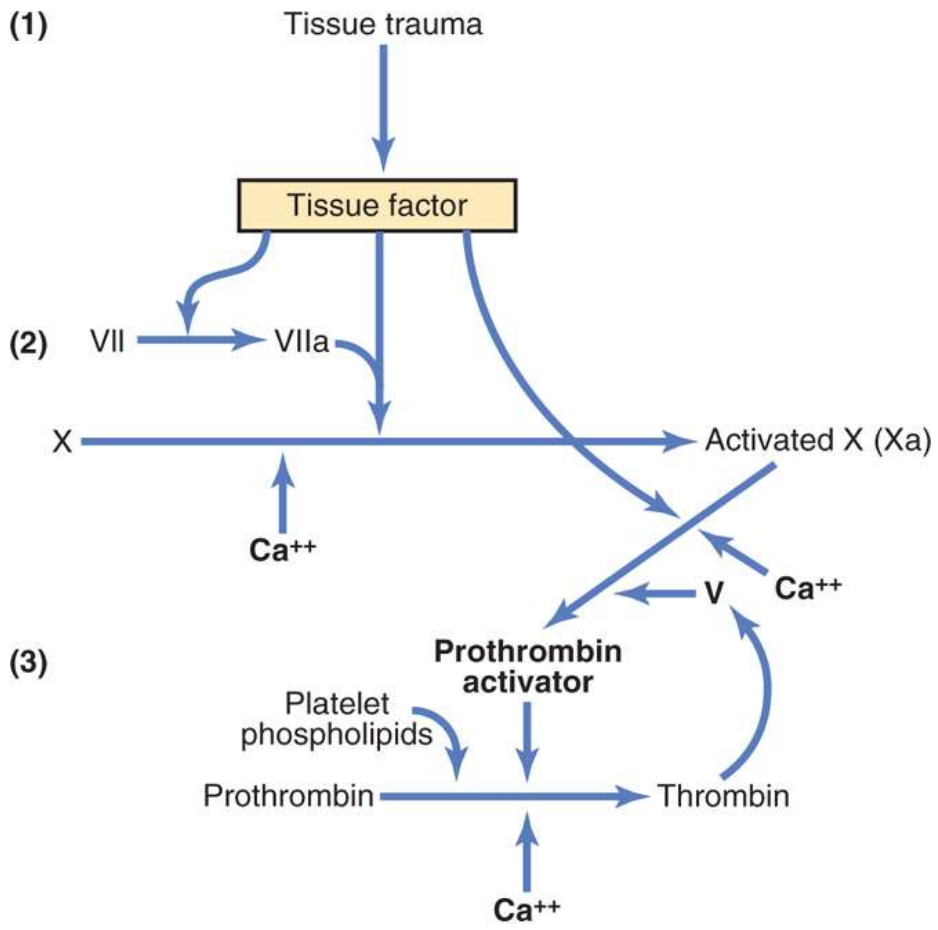


Figure 5 : Extrinsic pathway of coagulation[17]

Blood is exposed to these sub endothelial cells when vessel is damaged, and tissue factor on these cells then binds with factor VII. Thus factor VII is activated to factor VIIa. The complex of tissue factor and factor VIIa on the plasma membrane of the tissue cell then catalyses the activation of factor X. In addition, it catalyses factor

IX activation, which can then help activate even more factor X by plugging into the intrinsic pathway.(Figure 5)

In summary, theoretically clotting can be initiated either by the generation of the tissue factor or by factor XII activation. The two paths become one at the point of activation of factor Xa, which further acts as a catalyst in the transformation of prothrombin to thrombin. Thrombin aids in fibrin formation.

Thrombin also contributes to the activation of:

(1) factors XI and VIII in the intrinsic pathway; and

(2) factor V, with factor Va then serving as a cofactor for factor Xa.

Thrombin also activates platelets. As stated earlier, under physiological conditions; the two pathways just described actually are brought into play sequentially.[16]

(1)The *extrinsic pathway* is the traditional and major way of *commencing* coagulation in our body, and the intrinsic pathway plays minute role (in contrast to its initiation of clotting in wetable surfaces or, within the body in several unusual situations). Accordingly, thrombin is *primarily* generated only by the extrinsic pathway. The amount of thrombin is too small, however, to produce adequate and sustained coagulation.

(2) It is great enough, though, to initiate thrombin's positive-feedback effects on the *intrinsic pathway*—activation of factors XI and VIII and of platelets.

(3) Thus the intrinsic pathway gets activated independently of Hageman factor (factor XII), and this pathway then generates the large amounts of thrombin required for adequate coagulation. In essence, thrombin eliminates the need for factor XII.

Moreover, thrombin not only recruits the intrinsic pathway but facilitates the prothrombin-thrombin step itself by activating factor V and platelets. The name of the clotting factors is given in Figure 6.

Factor I	Fibrinogen
Factor II	Prothrombin
Factor III	Thromboplastin
Factor IV	Calcium
Factor V	Proaccelerin, labile factor
Factor VI	(no longer used)
Factor VII	Serum prothrombin conversion accelerator (SPCA), stable factor
Factor VIII	Antihemophilic factor (AHF)
Factor IX	Christmas factor, plasma thromboplastin component (PTC)
Factor X	Stuart Factor, Stuart-Prower factor
Factor XI	Plasma thromboplastin antecedent (PTA)
Factor XII	Hageman factor
Factor XIII	Fibrin stabilizing factor

Figure 6: Clotting Factors

Finally it should be noted that the liver plays several important indirect roles in clotting (Figure 7), and persons with liver disease frequently have serious bleeding problems. First, the liver is the site of production for various clotting factors. Second, the bile salts which are essential for normal intestinal absorption of the lipid-soluble substance **vitamin K** are produced from liver**.** [16]

Vitamin K is vital for mammals and for organisms that prepare food by photosynthesis. Plants are a dietary source of vitamin K for humans. In human beings, vitamin K is cofactor which is required for the γ-carboxylation of numerous elements involved in coagulation like Factor II, VII, IX, X and anticoagulant proteins. (Figure-8) This helps in proper of clotting factors, Ca^{2+}, and membrane phospholipids and modulator proteins. [18]

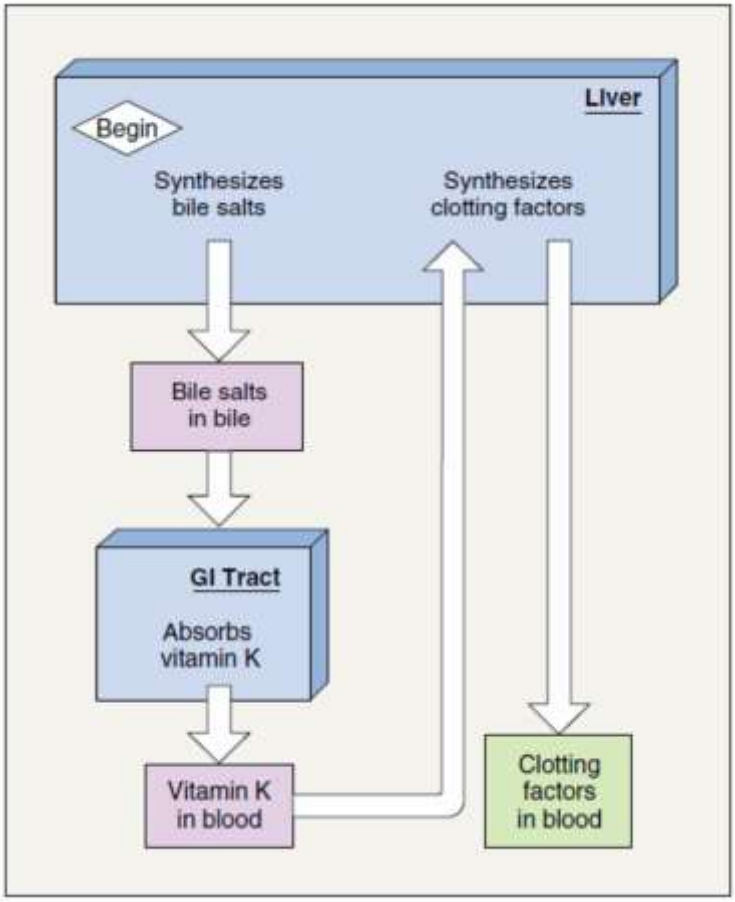


Figure 7 – Vitamin K synthesis[16]

Vitamin K_1, or *phylloquinone* (*phytonadione)* found in plants. It is the only natural vitamin K available for therapeutic use. Gram-positive bacteria synthesis

Vitamin K_2 (the *menaquinones*). In our body intestinal flora are the major source of vitamin K.

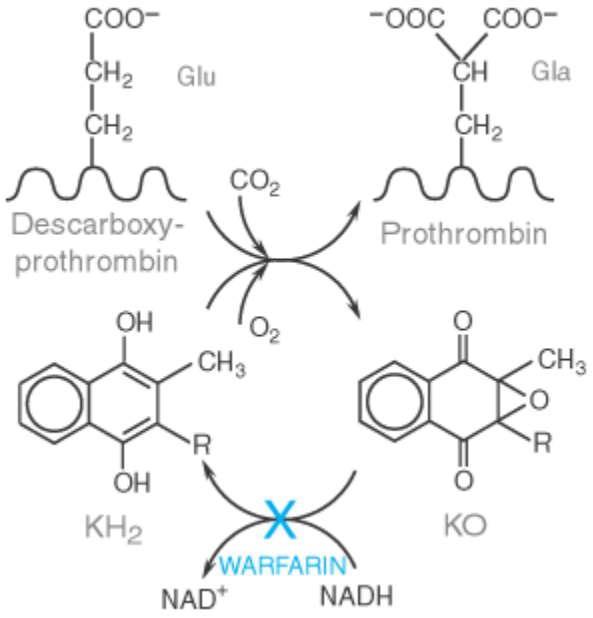


Figure 8 – Role of Vitamin K in the synthesis of Prothrombin

In normal animals and humans, phylloquinone and menaquinones are virtually devoid of pharmacodynamic activity. However, in subjects deficient in vitamin K, the vitamin performs its normal physiological functions like γ-carboxylation.[18]

FIBRINOLYTIC SYSTEM

Our body has mechanisms for limiting clot formation, itself, and for dissolving a clot after it has formed.

Factors that oppose clot formation

There are mainly three different mechanisms that oppose clot formation. Defects in any of these natural anticoagulant mechanisms are associated with abnormally high risk of clotting **(*hypercoagulability*).**

The first anticoagulant mechanism acts during the initiation phase of clotting and utilizes the plasma protein secreted by the endothelial cells called **tissue factor pathway inhibitor (TFPI).** This element fixes to tissue factor which get complexed with factor VIIa . Thus it inhibits the capability of these complexes to generate factor Xa. This anticoagulant mechanism is the reason that the extrinsic pathway by itself can generate only small amounts of thrombin.

The second anticoagulant mechanism is by **thrombomodulin** which is triggered by thrombin. Thrombin binds with thrombomodulin which is located in the endothelium as a surface receptor.

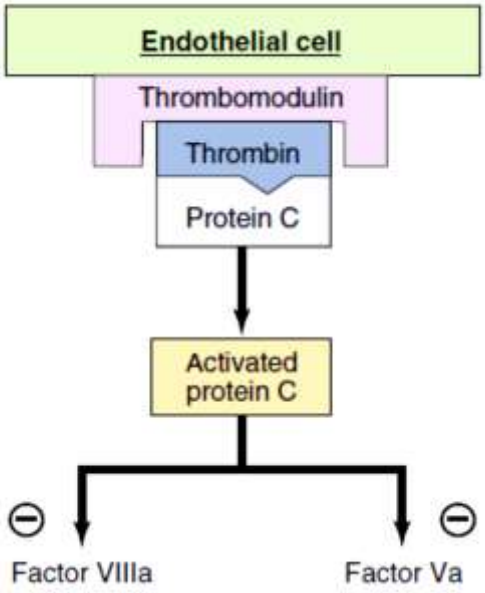


Figure 9 – Factors that oppose clot formation

This binding abolishes the entire clot generating effects of thrombin and thrombin – thrombomodulin complex binds to a plasma protein called **protein C.** This activates protein C. This also needs the existence of co-factor called Protein S. This activated protein C then causes proteolysis of factors VIIIa and Va. This is explained by figure 9.

A third naturally occurring mechanism that opposes the clot formation is by a plasma protein called **antithrombin III.** This antithrombin III binds with thrombin and inactivates it and inhibits the clot formation.

To do so, circulating antithrombin III must itself be activated, and this occurs when it binds to **heparin,** a substance that is present on the surface of endothelial cells.

Fibrinolysis

TFPI, protein C, and antithrombin III are some of the factors that oppose clot formation and limit the size of the clot. The fibrinolytic system *dissolves* a clot *after* it is formed.

It constitutes a proenzyme named as **plasminogen** which is present in the plasma**.** Plasminogen is activated to **plasmin** by protein **plasminogen activators.** Once plasmin is formed, it digests fibrin, thus promoting clot lysis. There are many types of plasminogen activators and numerous inhibitors (PAI-1 , PAI-2 etc.) of these plasminogen activators. One best example is the particular plasminogen activator known as **tissue plasminogen activator (t-PA).**[16]

Endothelial cells secrete this t-PA. During the mechanism of clot formation, both plasminogen and t-PA bind to fibrin and become integrated all through the clot. The binding of t-PA to fibrin is essential because t-PA is an enzyme which is very weak in the absence of fibrin.

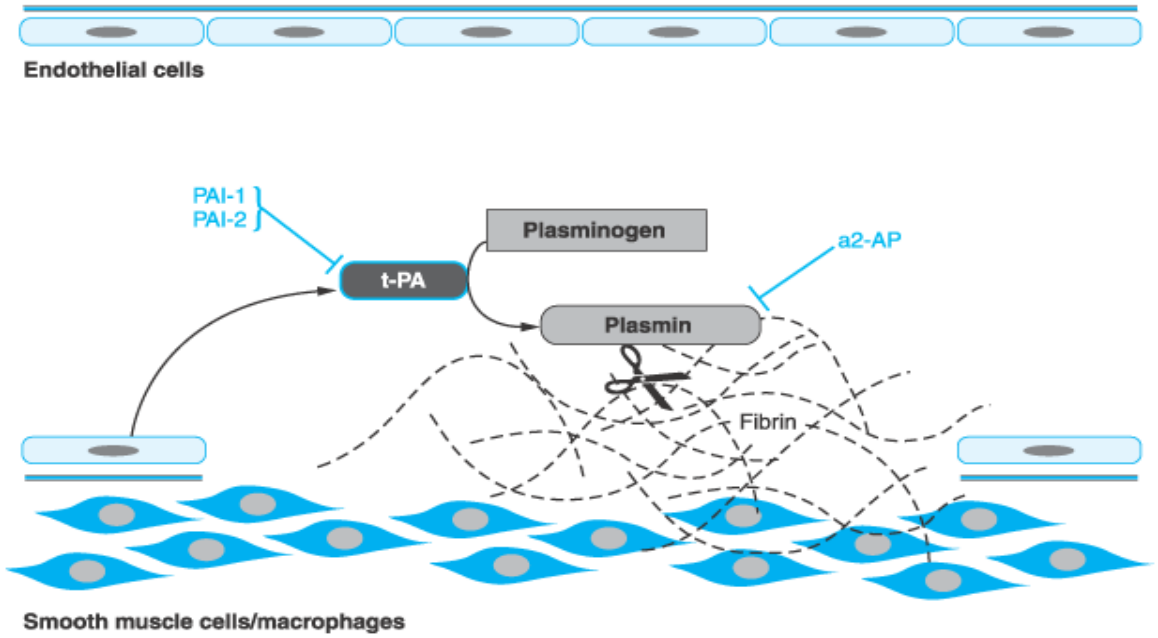


Figure 10 – Fibrinolytic system [18]

The presence of fibrin greatly surges the capacity of t-PA to convert the plasminogen to plasmin. (Figure - 10). Thus, fibrin is a key initiator of the fibrinolytic process that leads to its own dissolution. The secretion of t-PA is the last of the various anticlotting functions exerted by endothelial cells.[16]

LABORATORY PARAMETERS

- **COAGULATION PROFILE**

Bleeding Time

Standard incision should be made on the flexor aspect of the forearm. Bleeding time is a measure of time till the incised wound bleeds. Cessation of bleeding is dependent on a sufficient number of platelets, the its adhesion via adhesion molecules such as vWF and fibrinogen.[19] However, this test do not distinguish between defects in the vessel wall, thrombocytopenia, and platelet dysfunction.[20] Normal bleeding time is 1 to 6 minutes. [16]

Bleeding time was not effective to use it as screening test. It should also be noted that normal bleeding time does not exclude a bleeding disorder. This was published by American Society of Clinical Pathologists [21]

Clotting Time

Clotting time can be determined by several methods. Blood is collected in a clean glass test tube and the tube is moved back and forth at about 37°C about every 30 seconds until clotting occurs. By this method, the normal clotting time is 6 to 10 minutes.[17]

Platelet Count

Platelets help in the formation of platelet plug which helps in initial hemostasis. Thrombocytopenia can result in bleeding from microvasculature. In patients who

received massive blood transfusion, the platelet count should be maintained at 50,000/mL or higher. This decreases microvascular bleeding.[12,22] In previous studies with trauma patients have demonstrated attenuation of platelet stimulation to ADP agonist for patients in haemorrhagic shock [23], and after head injury [24] there is also the diminished platelet response to ADP, more prominent in nonsurvivors than survivors after life-threatening injury.[25]

Prothrombin Time (PT)

The integrity of extrinsic pathway of coagulation and common pathway involved in coagulation can be established by the Prothrombin time. To determine prothrombin time, excess tissue factor (tissue thromboplastin) is added to plasma. This test circumvents the intrinsic pathway. As the tissue thromboplastin contains phospholipids, it can act as a substitute for platelet. Thus the results of this test are not affected by decreased platelet count. PT can be used to control oral anti-coagulant therapy. When the plasma levels of one of the factors involved in these two pathways are <10% of normal, PT gets prolonged. It is more sensitive to deficiencies of factors VII and X.[26]

With most of the rabbit thromboplastin (thromboplastin obtained from rabbit brain) the normal range of the PT is between 11 and 14 seconds; when recombinant human thromboplastin is used, the range becomes shorter (10–12 seconds).[19]

Activated Partial Thromboplastin Time (aPTT)

The activated partial tissue thromboplastin time (aPTT) is a coagulation test which checks defect in intrinsic pathway and common pathway of blood clotting mechanism. Plasma and a phospholipid platelet substitute (partial thromboplastin) are mixed, recalcified, and the rate of formation of fibrin is noted as end point. This needs the factors involved in the intrinsic pathway and the factors of common pathway to be present in normal amounts. This forms the basis of aPTT.[27]

Platelet substitutes are powerless to activate the extrinsic pathway, which requires complete tissue thromboplastin (tissue factor). Thus, the aPTT does not get changed in factor VII deficiency.

Factor VIII and IX deficiencies can be easily picked up by aPTT than factors of intrinsic pathway and common pathway. This test becomes abnormal only if the plasma level of any one of the factors mentioned above is <15% to 30% of the normal value.[27-28]

The normal range is typically 26–40 seconds. The common causes of a prolonged aPTT are as follows:

1. Diseases affecting liver
2. Disseminated intravascular coagulation
3. Transfusion with red blood cells alone (plasma- depleted)
4. Administration of heparin or other anticoagulants
5. A circulating anticoagulant (inhibitor)

6. Deficiency of a coagulation factor other than factor VII.

The aPTT gets prolonged moderately with oral anticoagulant therapy and in vitamin K deficiency.[19]

Fibrinogen

Fibrinogen is a large dimeric protein; each monomer consists of three polypeptides like Aα, Bβ and γ which are held together by 12 disulphide bonds. Fibrinogen is derived from endocytosis of plasma fibrinogen mediated by glycoprotein IIb IIIa and get stored in alpha granules. Fibrin is formed from fibrinogen by thrombin cleavage releasing the A and B peptides from fibrinogen.[29]

The principle behind the Fibrinogen Assay by Clauss Technique is as follows. Strong thrombin solution is added to diluted plasma (The plasma must be diluted so that, inhibitors like FDPs and heparin also get diluted). A strong thrombin solution is also a major requisite to be used so that the clotting time is independent of the thrombin concentration.[30] The normal range is approximately 1.8–3.6 g/l or 200 to 400 mg/dl.[31]

- **MARKERS OF FIBRINOLYSIS**

Fibrin Degradation Products (FDP)

The proteolytic action of plasmin on fibrinogen yields Fibrin degradation products (FDPs). DIC and fibrinolysis are associated with Plasma levels of are increased FDP.[32] Healthy subjects have an FDP concentration of less than 10 mg/ml.

Concentrations between 10 and 40 mg/ml are found in acute venous thromboembolism, acute myocardial infarction and after major surgery. High levels are seen in systemic fibrinolysis associated with DIC and thrombolytic therapy with streptokinase.[19]

D – Dimer

D-dimer is a non-invasive and rapid test routinely used to evaluate for pulmonary embolism.[33] But it has low specificity and this limits the usefulness of D-dimer testing. Specificity of this test is between 40% and 60% and this can lead to more number of false- positive results.[34] Increased fibrinolysis in trauma patients proved to be correlated with the severity of injury.[35] Whenever there is aggressive fibrinolysis, it manifests as increase in D-dimer levels. Thus the blood clot becomes soluble. Subsequently, exhaustion of coagulation factors and fibrinogen leads to the development of disseminated intravascular coagulation (DIC).[36]

Normal levels should be less than 200 mg/ml.[19] Positive D-dimer can be in Pulmonary Embolism, deep vein thrombosis (DVT), old age, malignancy, and pregnancy.[37-43]

- **BASE DEFICIT INDICATORS**

Arterial Blood Gas Analysis

Arterial blood gas is used to measure the following parameters:

- pH
- PCO_2
- PO_2
- CO_2
- $[HCO_3^-]$

Normal values for Arterial Blood Gas Analysis

- $[HCO_3^-]$ → 22–30 meq/L
- PCO2 → 32–45 mm Hg
- pH → 7.35–7.45
- PO2 → 72–104 mm Hg [44]

Base excess or base deficit

Total amount of base (in mille moles) that is needed to titrate one liter of blood in arteries to 7.40 as pH is known as base deficit. In 1960 Anderson and Engel were the first people who recommended that Base deficit can be used to find the extent of metabolic acidosis. Modified Van Slyke equation is used to find the standard base deficit (BD).[45]

Previous studies have correlated base deficit with severity of injury and amount of blood loss based on data from both animals and human beings.[46-50]

The base deficit can be used as an indicator of severity of illness because in hemorrhage and hypotension, oxygen delivery to the tissues becomes insufficient.

This forces the inception of anaerobic metabolism which causes lactic acid to accumulate.[51] Large amounts of iv fluids administration during resuscitation can also affect the base deficit .[52]

Serum Lactate

Lactate levels can be used as a surrogate to assess the severity of illness and to measure the response to therapeutic interventions.[53] Lactate is produced in highest level in muscle even though it is formed by most tissues. [54-55] Under normal conditions, liver clears lactate from the blood rapidly, with a small amount of additional clearance by the kidneys.[54,56]

Normal value:

- Lactate in arterial blood 0.5–1.6 mmol/L or 4.5–14.4 mg/dL
- Lactate in venous blood 0.5–2.2 mmol/L or 4.5–19.8 mg/dL [44]

Hypoperfusion as a result of blood loss, is common amongst patients with trauma.[57] The presence of vital sign abnormalities may help to identify shock but their absence does not exclude occult hypoperfusion.[58] Elevated lactate levels may help to identify concealed ongoing tissue hypoperfusion.[59]

The level of lactate elevation and lactate clearance rate correlates strongly with the risk of multi-organ dysfunction and mortality after trauma. Lactate clearance can also be used as an endpoint to guide resuscitation. [60 -62]

ETIOLOGY OF TRAUMATIC COAGULOPATHY

The coagulopathy in trauma is complex in origin. Frequently, they are caused by interconnected factors. Some of them are specified below

Etiologies

- Clotting factors dilution
- Hypothermia
    - Enzyme function of coagulation factor get reduced
    - dysfunction of Platelet
    - Increased Fibrinolysis
- Trauma
    - Head trauma can result in Disseminated Intravascular Coagulation
- Warfarin therapy
- Liver diseases
- Coagulation disorders like
    - Haemophilia
    - von Willebrand disease[63]

Dilution

It is apparent that when enormous intravenous fluid and packed cells are transfused to the patients, the coagulation factors in the plasma will be diluted.[64] Many studies have already proven that dilution is often not a problem until the patient is infused with 10 to 12 units of red cells [65- 66.]

Hypothermia

Patients with traumatic injury are liable to hypothermia.[67,68] Patients may be at accidental site for a long period of time and may present with hypothermia on admission.[69] Infusion of one unit of packed red cells stored at 4°C can decrease the core body temperature by 0.25°C.[70] When the i.v fluids are infused at room temperature, for every litre infused the temperature is lowered by 0.5°C. Exposure of visceral organs at the time of surgery can result in profound hypothermia. Hypothermia has intense effects on the coagulation which can in turn result in clinical bleeding.[67, 71, 72] Enzymes required for coagulation are temperature dependent. Even mild cooling can render the patient coagulopathic by affecting the enzymatic reactions.

Rohrer showed that the activated partial thromboplastin time (aPTT) prolonged to 39 seconds at 34°C and to 46 seconds at 31°C from normal 36 seconds at 37°C .[73] Submissive hypothermia can affect functions of platelet. It can also kindle fibrinolysis. Thus, bleeding can be increased significantly even with modest hypothermia.[71, 74]

Trauma

The main stimulus for blood coagulation is tissue injury.[75- 76] Patients with severe injuries to brain frequently have severe defibrination due to the release of thromboplastin from brain tissue. These patients will suffer from relentlessly disturbed haemostasis characterized by plasma fibrinogen less than 50 mg/dL. They may have DIC and this can lead to increased blood products transfusion.

As coagulation factors are synthesized in liver, severe liver injury or significant shock can also lead to failure to compensate for consumption of coagulation factors. [77- 78]

Underlying disease

Haemophilia patients may have significant bleeding with their injuries. Patients taking oral anticoagulants, patients with liver disease are challenging and have ominously higher mortality with trauma.[79-80] Patients suffering from liver disease have several coagulation defects.[81] Liver synthesize many coagulation factors and inhibitors, except factor VIII and vWF. Liver disease can be associated with decrease in plasma levels of inhibitors of fibrinolysis.

Most common inherited coagulation defects is von Willebrand disease, which is associated with tireless bleeding subsequently after trauma.[82] One in 10,000 male patients is having haemophilia.[83] These patients may continue to bleed unless particular deficient factor replacement is given.

Approximately 1% of the population are on anticoagulation therapy with warfarin. Warfarin treatment has higher morbidity and mortality when they present with intracranial haemorrhage was reported by several studies.[84 - 85]

PATHOPHYSIOLOGY OF TRAUMATIC COAGULOPATHY

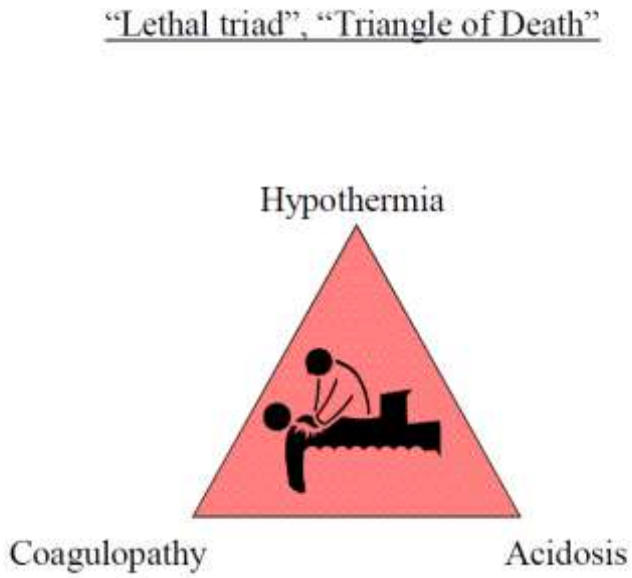


Figure 11 – Lethal Triad or triad of death

Hypothermia

Normal human body temperature is between the range of 35.6 – 37.8˚C. Core temperature < 35˚C can be defined as hypothermia.[86] Core temperature < 32° C can result in 100% mortality irrespective of degree of shock, injury severity or volume of iv fluids administered. This was already proven by a study.[87] Even mild hypothermia can alter the coagulation system in trauma patients.[88] As already explained, the coagulation involves various temperature and pH-dependent complex enzymatic reactions.[89]

Coagulopathy can be defined as a comprehensive group of disease states that results in decreased capability of this coagulation system.[86] It has been established that

hypothermia decreases the body's ability to arrest bleeding. This may due to platelet dysfunction, coagulation system, and incongruous activation of clot breakdown.

Hypothermia in trauma can occur due to many factors. Hemorrhagic shock and traumatic brain injury can impair the regulation of core body temperature.[89]

Normal saline at room temperature is hypothermic when compared to our body temperature. Thus, resuscitation with huge volume of IV fluids in room temperature can significantly contribute to hypothermia and death.

Acidosis

A pH level is a measure of H^+ concentration. A normal pH ranges from 7.35–7.45. This is maintained by equilibrium between hydrogen ions concentration (acids) and buffers. This balance is meticulously under the control of lungs and kidney.

Arterial pH < 7.35 is defined as acidosis. In patients with trauma the major cause for acidosis is tissue hypoperfusion. Anemia from hemorrhage, vasoconstriction of peripheral vessels due to hypothermia and hemorrhage can lead to inadequate oxygen delivery to the tissues. This creates a disproportion between oxygen demand and oxygen delivery. Thus, the cells in the body are enforced to use anaerobic metabolism which ends up in the lactic acid accumulation.[90]

Acidosis can occur in patients who are given normal saline which is an unbalanced crystalloid solution.[91] The pH of normal saline is around 5.5, which is extremely acidic than the pH 7.34 (arterial blood). Infusion of normal saline in large amount can result in hyperchloremic metabolic acidosis.[92] This can produce an added

effect on the existing lactic acidosis in trauma patients. Furthermore, it is also proven that increase in systemic tissue inflammation with excessive use of normal saline also support to the traumatic coagulopathy.[92] Ringer Lactate with pH 6.5 is discordant with several medications and blood products.

Lastly, hypoventilation due to obstruction to the respiratory passage or respiratory depression in a trauma patient may result in hypercapnia (increased CO_2 levels) and thus respiratory acidosis. Narcotic abuse, alcohol intoxication, traumatic injuries to brain, flail chest or previous history of lung diseases such as chronic obstructive pulmonary disease can also result in respiratory acidosis.

Severe acidemia (pH < 7.20), results in many disastrous consequences like impairment of coagulation system.[93] The decrease in pH from 7.4 to 7.0 reduced the efficacy of the coagulation system by 55–70% was proven already. [94]

Coagulopathy

Coagulopathy has a potential to create a continued hemorrhage in the bleeding trauma patient regardless of a specific cause.

Coagulopathy is associated with a four-fold increase in mortality.[8, 14, 95] This can occur due to several causes like hypothermia, acidosis, clotting factors loss through bleeding, hemodilution, and the utilization of clotting factors by our body and following that there occurs depletion of both platelets and clotting factors.[90]

Infusion of normal saline and packed red blood cells in huge amount further dilutes the residual clotting factors in the circulation. In addition there occurs abnormal activation of the clotting cascade, causing undue formation of blood clot and

increased fibrinolysis. This occurs in disproportion to the injury in a patient with severe trauma.[91] Thus abnormal activation of the blood coagulation system swiftly ingests the left out clotting factors in the body. This further leads to augmented deficiency of the important factors required to achieve hemostasis.

The exact mechanism behind this coagulopathy is systemic anticoagulation due to protein C activation and enhanced fibrinolysis.

Protein C Activation

Brohi.K et al showed that hypoperfusion is directly proportional to the severity of injury and associated with thrombomodulin increase and protein C decrease.[6]

Theoretically, trauma activates the extrinsic pathway in the absence of hypo perfusion as shown in Figure12.

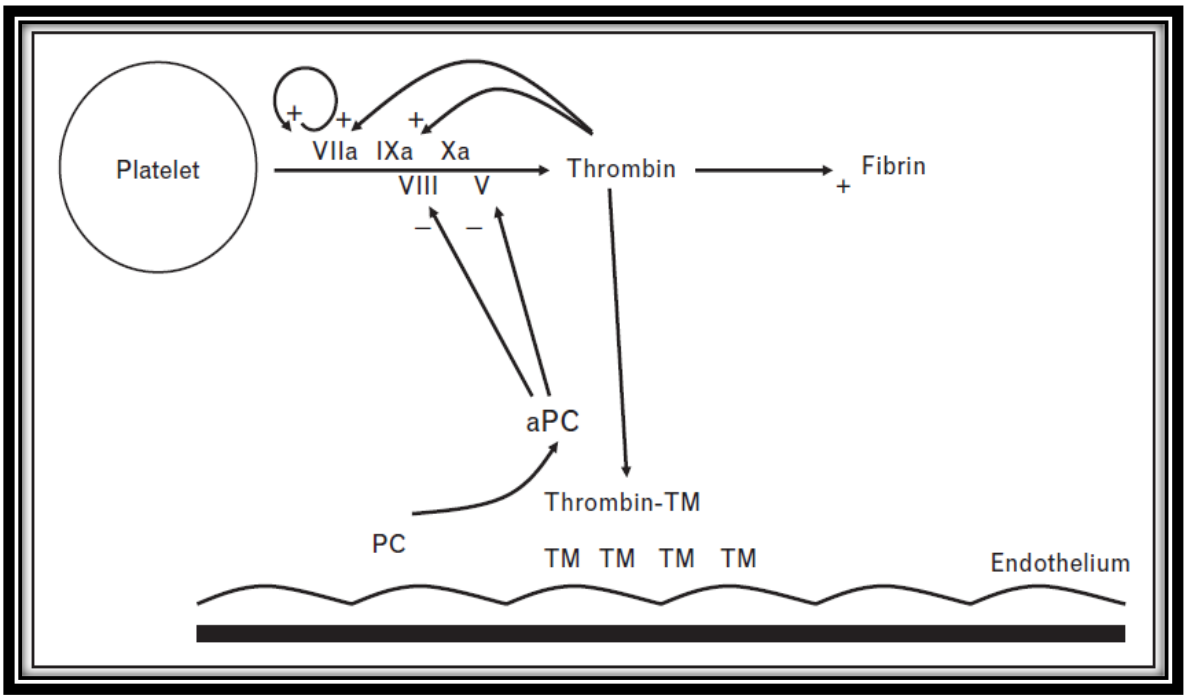


Figure 12 : Mechanism of Acute Traumatic Coagulopathy

In the existence of tissue hypoperfusion, thrombomodulin and thrombin complex distract it to act as an anticoagulant. This complex activates protein C. Protein C gets activated and inhibits the extrinsic pathway by causing proteolysis of factor V and VIII (Figure 13). [96.]

Enhanced fibrinolysis

Trauma can lead to enhanced fibrinolytic activity. Increased D-dimer levels following traumatic injury have been recognized by other studies.[6, 97] Release of tissue plasminogen activator (tPA) following injury results in fibrinolysis.[98-100] Regulator to diminish the propagation of blood clot to undamaged area is tPA. [6]

Tissue hypoperfusion decreases the level of plasminogen activator inhibitor-1 (PAI-1) . Activated protein C in excess will ingest more and more PAI-1[101] and thus leads to increased fibrinolysis. This is shown in Figure 13.[96]

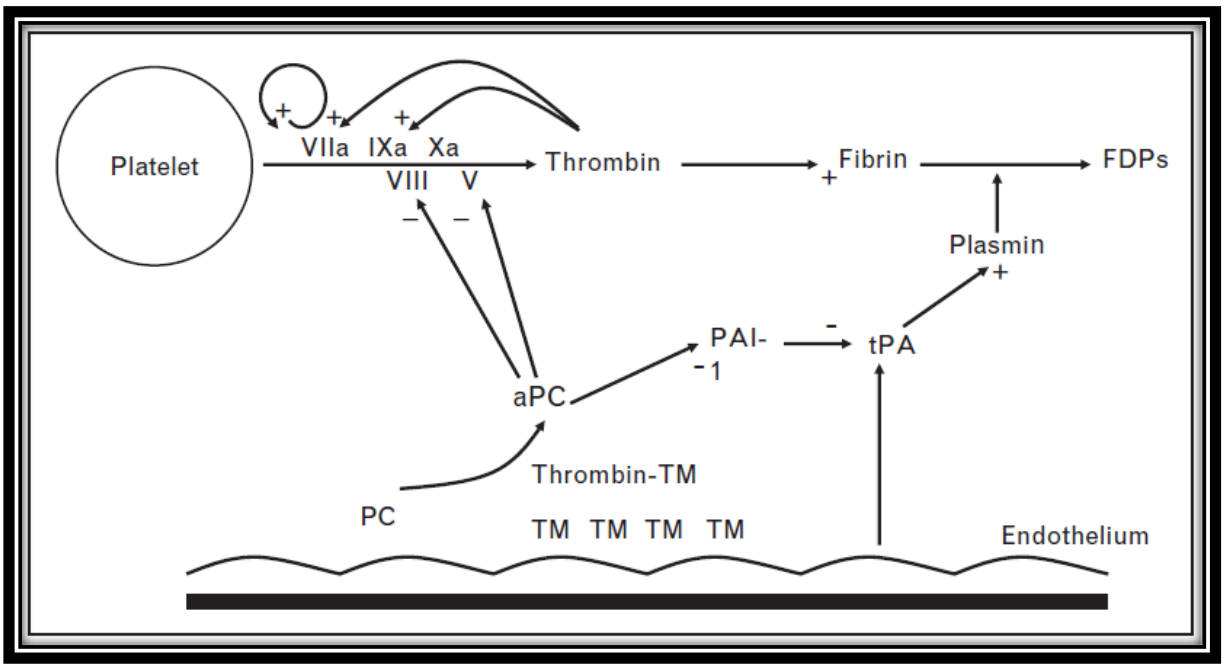


Figure 13 : Process of Hyperfibrinolysis

HISTORY :

John H Seigel et al (1990) studied the importance of variables like Glasgow Coma Score, base excess (or deficit), lactate level, Injury Severity Score and replacement of blood volume in patients with trauma. They conducted a study with 185 blunt liver trauma. Both base excess and initial 24-hour volume of blood transfusion reflected the probability of death and found to be highly significant. This was tested on data from 323 additional patients showed it to be a highly significant early predictor of outcome. [102]

Davis J W et al (1996) observed that the transfusion requirements increased significantly as the Base Deficit category became more severe.. Both ICU and period of stay in hospital increased significantly with worsening Base Deficit. They also reported that as the base deficit increases, the total number cases with shock – related complications also increased significantly. They also found that as the Base Deficit worsens, mortality also increased significantly.

Thus they concluded that Base Deficit on admission identifies patients who may require early blood transfusion and increased stay in ICU and hospital, and may easily develop shock-related complications.[49] They have not taken into account the severity of injury as they included all patients who required blood transfusion.

Cosgriff et al (1997) analysed patients who received blood transfusion greater than 10 units of packed red cells for 24 hours. According to this study, 27 patients (47%) developed life – threatening coagulopathy. They found the following 4 factors as risk factors

1. Temperature less than 34°C
2. pH less than 7.10
3. Systolic Blood Pressure less than 70 mm Hg
4. Injury Severity Score (ISS) more than 25

They also found that the probability of developing coagulopathy was 49% when there was ISS of more than 25 and Temperature less than 34°C ; with ISS of more than 25 and pH < 7.10 the incidence of coagulopathy was 49%; When all the four risk factors mentioned above are present he incidence was 98%.[103]

Thus they concluded that coagulopathy in the utterly injured patients who require massive blood transfusion can be well predicted by progressive metabolic acidosis and persistent hypothermia. They have not mentioned about the severity of injury and for acidosis they have taken blood pH alone. Base deficit was not taken into consideration.

Brohi K et al (2003) wanted to prove that traumatic coagulopathy can be caused principally by IV fluids administration and hypothermia. They observed that 57.7% patients had an ISS of more than 15; 24.4% of patients had a substantial coagulopathy and they also had ominously increased mortality. The incidence of coagulopathy increased with injury severity, but was not related to the volume of IV fluids given to the patients. They concluded that traumatic coagulopathy is an indicator of severity of injury and it is related to mortality.[95]

They have not considered the fluid administered before hospitalisation which may alter the coagulation status.

Macleod et al (2003) showed that there were 8.9% overall mortality due to all causes. 28% had a prolonged PT and 8% had an abnormal aPTT on arrival to the trauma care centre. In patients with normal PT, 6.3% died, as compared with 19.3% with an abnormal PT which was statistically significant. They also reported that the PT and aPTT can be used as independent predictors of mortality whereas platelet count cannot be used.

Thus they concluded that the frequency of coagulation abnormalities is high early after trauma and coagulopathy can be used as an independent predictor of mortality.[8] They have not considered the markers of fibrinolysis to diagnose coagulopathy.

Marc Meagle et al (2006) observed that 34.2% had coagulopathy. The incidence for coagulopathy was also increased as the amounts of IV fluids administered increased. 29% of patients with coagulopathy developed multi organ failure which was also found to be statistically significant.[14]

Karim Brohi et al (2007) conducted a prospective study with a cohort of 208 major trauma patients. They found that the patients without tissue hypoperfusion didn't have coagulopathy, irrespective of thrombin generated. Prolonged aPTT and PT were detected with an augmented Base Deficit. They also published that the increasing Base Deficit and mortality was related with high thrombomodulin and decreased protein C. They concluded that in the presence of tissue hypo perfusion traumatic coagulopathy occurs early.[6]

Park et al (2008) conducted a study with 53 patients. Among these 15 patients died. They proved that the combined use of markers of coagulation and standard clinical indices will help to predict the mortality irrespective of type of injury (burned and non-burned)[104]

Duchesne et al (2009) conducted a study of patients with diagnosis of TIC after packed cells transfusion of more than 10 units during surgery. They concluded that Trauma Induced Coagulopathy is very common after severe injury and also associated with mortality in patients who had transfusion of more than10 units. [105]

Hess et al (2009) conducted a study with trauma patients and found that abnormal coagulation tests were increasingly reported as the severity of injury increases. The abnormal PT ranges from 5% to 43% as the Injury Severity Scores increased from 5% to over 45%. Low platelet counts were from 4% to 18 %. Abnormalities in coagulation tests were associated with significant mortality and this was proved to be true for the aPTT.[106]

Victor Jeger et al (2010) studied patients with an Injury Severity Score (ISS) of more than or equal to16. They found that out of the 172 patients 32.6% had Traumatic coagulopathy at the time of admission .[107]

Kanchana Rangarajan et al (2010) studied 48 orthopaedic trauma patients. Coagulation parameters and DIC score were evaluated. Out of 48 patients, 20% had mild increase in DIC scores at the time of admission. Fibrinogen levels alone were significantly increased in these patients from the time of admission. No change was found in the remaining parameters.[108]

Sjoerd Greuters et al (2011) conducted a study in patients who had Traumatic Brain Injury (TBI) alone. Among these patients 24% suffered from early coagulopathy. Thus they confirmed that presence of coagulopathy had been related to worse clinical outcome.[109]

Johansson et al (2011) wanted to investigate the occurrence of overt DIC and acute traumatic coagulopathy of shock based on their biomarkers reflecting tissue/ endothelial cell/ glycocalyx damage. They reported that 15% had acute traumatic coagulopathy whereas no patients had overt DIC. Patients with acute traumatic coagulopathy had higher ISS, increased blood transfusion requirements and significant mortality. One important finding in this study was with patients without acute traumatic coagulopathy, had the same report of biomarkers as that observed in patients with acute traumatic coagulopathy.[110]

Bernard Floccard et al (2012) conducted a study which shows that 56% patients had abnormal coagulation tests on scene screening for coagulation profile. Activity of Protein C was decreased in patients with coagulopathy group which was proved to be significant statistically. 60% of patients had abnormal coagulation tests on hospital admission. They concluded that Coagulopathy occurs even prior to hospital admission after injury that is before fluid administration. The incidence of coagulopathy is high at the accidental site and is related to the injury and not to hypoperfusion.[111]

Erick Mujuni et al (2012) observed that coagulopathy incidence was 54%. The ISS mean for the patients with coagulopathy was little higher. Patients with

coagulopathy stayed longer in hospital. Coagulopathy was also associated with acute renal injury .Mortality was more in the coagulopathy group. They concluded that coagulation profile can be used to predict outcomes in major trauma patients.[112]

Vijay kanna et al (2013) studied that the Traumatic patients and showed the incidence of coagulopathy as 60% in patients with head injury and early blood transfusion reversed back the abnormality in coagulation profile.[113]

Fei A et al (2015) conducted a study to assess the prognostic value of haemostasis-related parameters in patients admitted in ICU. They conclude that FDP is the best self-determining pointer of mortality in ICU patients among all other parameters examined. When FDP and APACHE II scores were used in concordance, it may help to predict mortality in ICU patients.[114]

Delano MJ et al (2015) wanted to study the effect of recovery when hypertonic solutions were used for coagulopathy after trauma. When patients in shock got treated with Normal saline, Tissue factor (TF) was found to be elevated. But when treated with hypertonic saline and hypertonic saline with dextran TF was found to be decreased. Thus they concluded that when hypertonic saline with Dextran are administered during resuscitation it worsens coagulability and may result in increased fibrinolysis in patients with haemorrhagic shock after trauma.[115]

MATERIALS AND METHODS

TYPE OF STUDY :

Prospective Cohort study

SAMPLE SIZE :

60 (convenient sample)

STUDY PERIOD :

January 2014 to December 2014

TIME LINE OF THE STUDY

(From the inception to the end of the study using Henry Gantt Chart)

WORK DONE	2013	2014	2014	2015	2015
	Oct - Dec	Jan - Jun	Jul - Dec	Jan- May	Jun - Sep
Protocol Preparation					
Ethical Clearance					
Review of Literature					
Data Collection					
Data entry and Analysis					
Thesis Report Writing					
Thesis Submission					

STUDY SETTING :

This study was carried out with patients who get admitted in Causality department of Chennai Medical College Hospital and Research Centre, after obtaining Institute Ethical Committee approval.

INCLUSION CRITERIA :

- Age – 20 to 60 years.
- New Trauma case.
- Glasgow Coma Scale of more than 8/15.

EXCLUSION CRITERIA :

Patients with the following history are excluded.

- History of Diabetes Mellitus with Chronic Renal Failure and Hypertension with Chronic Renal Failure
- History of liver and cardiac diseases.
- History of anticoagulant treatment at present.
- History of valve replacement surgeries.
- History of taking medications which influence the coagulation profile.

PARAMETERS STUDIED :

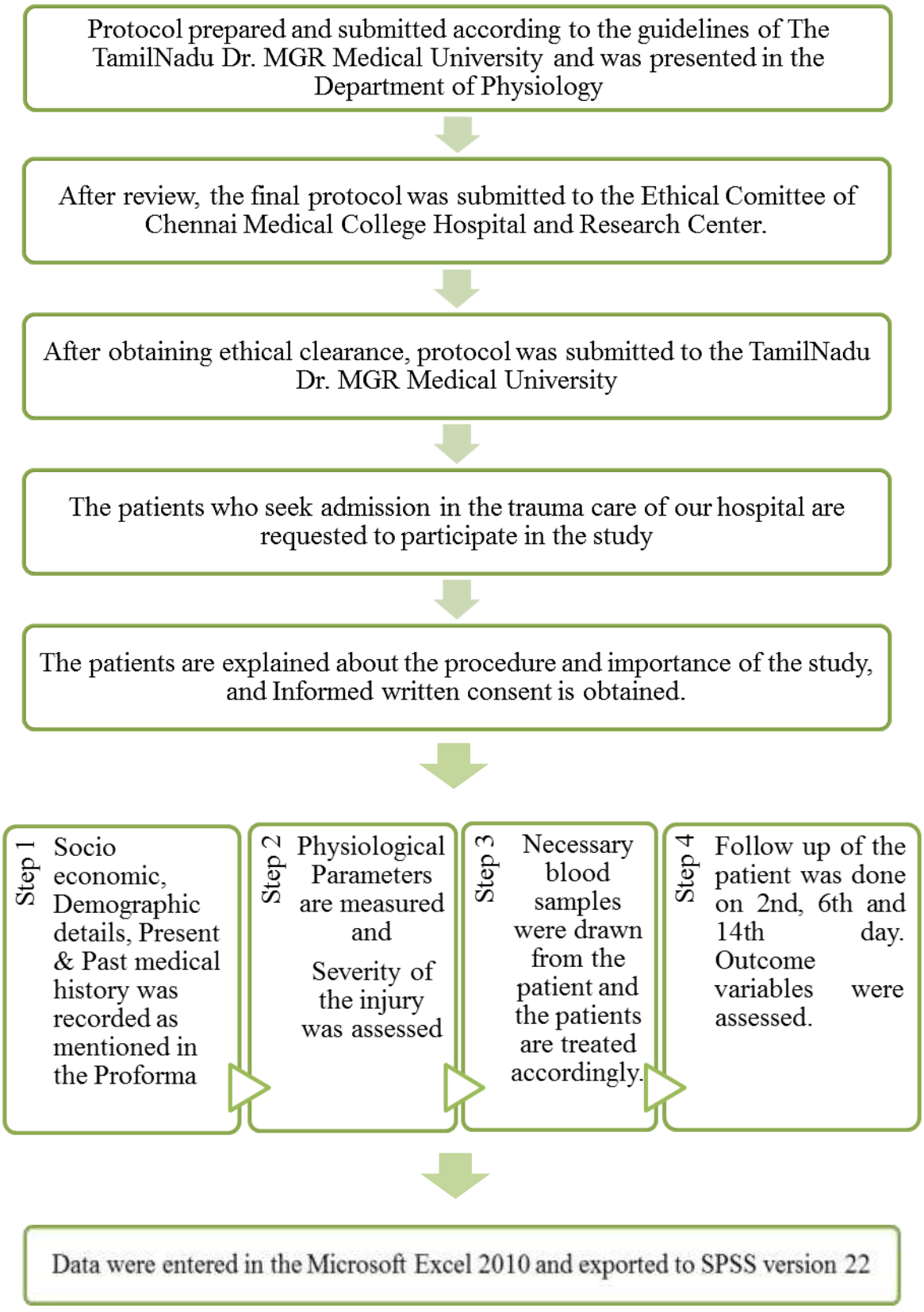
Revised Trauma Score (RTS) is employed to assess the injury severity which includes three physiological parameters:

- Respiratory rate **(RR).**
- Glasgow Coma Scale **(GCS)** and
- Systolic blood pressure **(SBP)**

- **PHYSIOLOGICAL PARAMETERS**
    - Body temperature
    - Pulse rate
    - Respiratory rate
    - Blood pressure

- **BIOCHEMICAL PARAMETERS**
    - Blood Urea
    - Serum Creatinine
    - Bleeding Time
    - Clotting Time
    - Platelet counts
    - Prothrombin Time (PT)
    - Activated Partial Tissue Thromboplastin Time (aPTT)
    - Fibrinogen level
    - Presence of Fibrin Degradation Products (FDP)
    - D – Dimer positivity
    - Arterial Blood Gas Analysis
    - Serum Lactate

STUDY TECHNIQUE:



STUDY PROCEDURE :

At the time of admission, after initial stabilization informed written consent was got from the patient or his/her relative. Then history was recorded patients were included in the study according to the inclusion criteria and exclusion criteria mentioned above.

General examination of the patient was done. Vital signs like Temperature, Pulse rate, Respiratory rate, and Blood Pressure were recorded manually. Patient was assessed and Glasgow Coma Scale was calculated. Then Revised Trauma Score –is considered by the following method [116]

RTS = 0.9368 GCS + 0.7326 SBP + 0.2908 RR

COAGULATION TESTS:

Bleeding time is determined by Duke's method. Bleeding Time greater than 6 mins is regarded as abnormal. [17]

Venous blood sample (3ml) was collected in vacutainer containing 3.8% trisodium citrate and 1 ml in a clean glass test tube.

Clotting time is determined by blood collected in a clean glass test tube. Then the tube is moved back and forth every 30 seconds until the blood is clotted. Clotting time more than 10 mins is considered to be abnormal.[17]

Blood samples were analysed to determine Platelet count using auto analyser. (Make - MINIDRAY Model No - 5300). Then remaining blood samples were centrifuged at 3000 rpm for 10 minutes to obtain clear plasma.

Coagulation profile (PT, aPTT) were done by using a coagulation semi – auto analyser (Make - Genera; Model no – 34).

Prothrombin Time (PT) was determined using a reagent named "LIQUIPLASTIN" a rabbit brain thromboplastin. 50 µl of plasma was taken and warmed at 37˚C for 2 minutes by keeping it in coagulation analyser. Then the 50 µl of rabbit brain thromboplastin reagent is added to the pre warmed plasma sample and again kept in the coagulation analyser. The reading given by the analyser is noted as the patient's Prothrombin time. Prothrombin Time more than 14 seconds is considered to be abnormal.[19]

Activated Partial Tissue Thromboplastin Time (aPTT) was determined using a reagent named " Hemostat aPTT - EL " a Ellagic Acid Activator. 50 µl of patient's plasma was taken and 50 µl of first reagent is added. Gently mixed and incubated for 3 minutes at 37˚C. Then second reagent is added by keeping it in the coagulation analyser. The reading given by the analyser is noted as the patient's aPTT. aPTT greater than 36 seconds is considered to be abnormal. [19]

Fibrinogen assay is done by clot based method using an automated coagulation analyser (STA Compact) and the normal value for fibrinogen is 200 to 400 mg/dL [30]

Fibrin Degradation Products are identified by Protamine sulphate method done manually. 500 µL of Plasma kept in the water bath at 37˚C for 2 mins. Then

50µL of 1 % Protamine sulphate is added. After 5 minutes the test tube is taken and watched for white precipitate. The presence of white precipitate indicates FDP positive. This test is based on the principle that it detects the presence of fibrin of Fibrin Degradation Products in Plasma. Fibrin acts with protamine sulphate and react within 15 minutes.

D – Dimer assay is done by chemi – luminescence assay technique. (Make - SNIBE MAGLUMINI; Model - 2000)

2ml arterial blood was collected in a heparinised tube and Arterial Blood Gas (ABG) analysis and Lactate was also done by the blood gas analyser. (Make: JEMPREMIER Model: 3000) From the ABG analysis report Base Deficit (marker of tissue hypo perfusion) was calculated using a formula mentioned below.[45]

$$\text{Base deficit} = 0.93 \times ((HCO_3^-) - 24.4 + 14.8 \times (pH - 7.4))$$

Base deficit or excess of 2 mmol /L (mEq/L) is considered to normal.[117] Base deficit > 6 mmol is previously termed as indicator of tissue hypoperfusion.[49] Arterial lactate > 1.6 mmol/L in arterial blood is considered as abnormal.[44]

Acute renal dysfunction in patients was assessed using Renal Function Test like Urea and Creatinine done using a semi – automated analyser.

Renal dysfunction was found by the formula given below.[118]

Renal function = Blood Urea Nitrogen (BUN) / Creatinine

Renal dysfunction is present if the value is greater than 20.

Blood Urea Nitrogen (BUN) is given by Blood Urea / 2.14

Patients with any of the following results in day 0 or day 2 were termed as coagulopathic.

- Bleeding Time > 6 mins
- Clotting Time > 10 mins
- Platelet count < 1.2 lakhs / cu. mm
- Prothrombin Time when prolonged for more than 14 seconds
- Activated Partial Thromboplastin Time more than 40 seconds
- Fibrinogen level of less than 200 mg per dL
- Positive Fibrin Degradation Product
- D - Dimer – positive.

The patients who are recruited into the study were monitored and studied on days 0, 2, 6, and 14. Outcome variables like mortality, renal dysfunction, Length of stay in hospital and routine physiological parameters were established and documented during these periods.

Patients were tracked upon till the time of discharge. Patients who were getting discharged during this period were considered to be survivors.

PHOTOS

METHOD OF STATISTICAL ANALYSIS

The data is entered in Microsoft Excel and exported to SPSS version 22. Appropriate statistical analysis is carried out by using Statistical Package for Social Science (SPSS). Both descriptive and inference statistical analysis is used to analyse the data. The descriptive data is presented as frequencies and proportions. The continuous data is presented as Mean with Standard Deviation. Univariate logistic regression is applied to establish the association between the independent variables and dependent (Outcome) variables like Morbidity, Mortality and complications like Acute Renal Injury. Those which are significant in univariate analysis were taken for multiple logistic regression model.

All the statistical analysis will be carried out at 5% level of significance and p value of less than or equal to 0.05 will be regarded as significant.

RESULTS

Totally 60 patients with both major and minor trauma were enrolled into the study from casualty between the months of January 2014 to December 2014. Their initial coagulation profile was determined and they were monitored up for two weeks to establish their primary clinical outcomes. Of these 2 patients (3.3%) got discharged against medical advice, moved to other hospital. Therefore only 58 patients were taken for analysis.

Demographic details and the socioeconomic details of the study population is given by table 1.

Table 1 : Demographic distribution of the data

PARAMETERS	**FREQUENCY** (n = 58)	**PERCENTAGE** (100%)
GENDER DISTRIBUTION		
Male	44	75.86 %
Female	14	24.13 %
AGE DISTRIBUTION (Based on age group)		
21 – 30 Years	18	31.0 %
31 – 40 Years	21	36.2 %
41 – 50 Years	6	10.3 %
51 – 60 Years	13	22.4 %

PARAMETERS	FREQUENCY (n = 58)	PERCENTAGE (100%)
OCCUPATIONAL STATUS		
Employed/ Salaried	24	41.1 %
Students	8	13.8 %
Business	9	15.5 %
Unemployed	17	29.3 %
EDUCATIONAL STATUS		
No education	8	13.8 %
Primary education	20	34.5 %
Secondary education	10	17.2 %
Graduate / higher	20	34.5 %

44 patients (76%) were male and 14 patients (24%) were female (Table 1) Patients were between age 20 and 60 years with a mean age of 38.53 $\pm$ 12.0 years. There were more number of patients in age group between 31 to 40 years.

The 34.5 % of the patients had primary education 34.5 % graduates or higher followed by 19 % had secondary education and 13.8 % patients were uneducated.

Table 2 : Distribution of other data

PARAMETERS	FREQUENCY	PERCENTAGE
TYPE OF INJURY		
Blunt Injury	48	82.8 %
Penetrating Injury	10	17.2 %
CAUSE OF INJURY		
Road Traffic Accident	39	67.2 %
Fall	10	17.2 %
Other cause of Injury	9	15.5 %
COAGULATION STATUS		
Coagulopathy Present	20	34.5 %
Coagulopathy Absent	38	65.5 %

Regarding the type of injury 10 patients (17.2%) presented with blunt injury the commonest and 38 patients (65.5 %) with penetrating injury. The mode of injury which had occurred commonly is Road Traffic Accident. This includes 39 patients (67.2 %), which is followed by fall from height 10 patients (17.2 %) and other mode of injury 9 patients (15.5%). Coagulopathy was present in 20 patients (34.5%)

Chart 1 : Status of Coagulopathy in the study population

regarded as

Table 3 : Status of Co-morbid conditions and Blood Transfusion

PARAMETER	FREQUENCY	PERCENTAGE

PARAMETERS	FREQUENCY	PERCENTAGE
BLOOD TRANSFUSION		
Given	17	29. 3 %
Not Given	41	70.7 %
DIABETES MELLITUS		
Present	17	29.3 %
Absent	41	70.7 %
HYPERTENSION		
Present	13	22.4 %
Absent	45	77.6 %

. In total blood transfusion was given 17 (29.3 %) patients. Overall 17 (29.3%) patients were diabetic and 13 (22.4%) patients were hypertensive patients

Table 4 : Distribution of Outcome parameters

ACUTE RENAL INJURY		
Present	7	12.1 %
Absent	51	87.9 %
MORTALITY STATISTICS		
Dead	6	10.3 %
Survived	52	89.7 %
LENGTH OF STAY IN (Based on No. of Patients who survived – (52))		
Greater than or equal to 11 days	30	57.7 %
Less than 11 days	22	42.3 %

Among 58 patients, 7 (12.1%) patients had acute renal injury based on the ratio of Blood urea nitrogen and Serum creatinine.

Overall mortality is 10.3% i.e 6 (15.5%) patients in the study population. 9 patients had base deficit > 6 mmol /L and suffered from tissue hypoperfusion and 49 patients had Base deficit below 6 mmol/ L.

Morbidity was assessed using the total length of stay of the trauma patient either in the ward or ICU. For this analysis, the patients who survived during the follow up period were only included. Median was found to be 11 for the extent of stay in hospital (days). Then the patients were categorised into < 11 days and $\geq$ 11 days. 30 (57.7%) patients stayed for $\geq$ 11 days and 22 (42.3%) patients stayed for less than 11 days.

Table 5 : Distribution of different parameters of Coagulation profile

Parameters Studied	**Normal Results No. of Patients**	**Abnormal Results**	**Mean $\pm$ SD**

	(%)	No. of Patients (%)	
COAGULATION PROFILE			
Platelet Count	49 (84.5%)	9 (15.5 %)	2.22 ± 0.35
Bleeding Time	54 (93.1 %)	4 (6.90%)	4.10 ± 0.28
Clotting Time	49 (84.5 %)	9 (15.5%)	6.81 ± 0.26
Prothrombin Time	38 (65.5 %)	20 (34.5%)	14.1 ± 0.32
aPTT	49 (84.5 %)	9 (15.5 %)	31.32 ± 0.25
Fibrinogen	49 (84.5%)	9 (15.5 %)	271.34 ± 16.48

Out of 58 patients, 49 patients had normal Platelet count & 54 patients had normal Bleeding Time and only 9 patients had low platelet count and 4 patients had prolonged bleeding time. 20 patients (37.5 %) out of 58 patients with trauma had elevated PT. A total of 9 patients had elevated aPTT. 9 (15.5%) patients had decreased fibrinogen

Chart 2 : Status of coagulation Profile and D – Dimer results

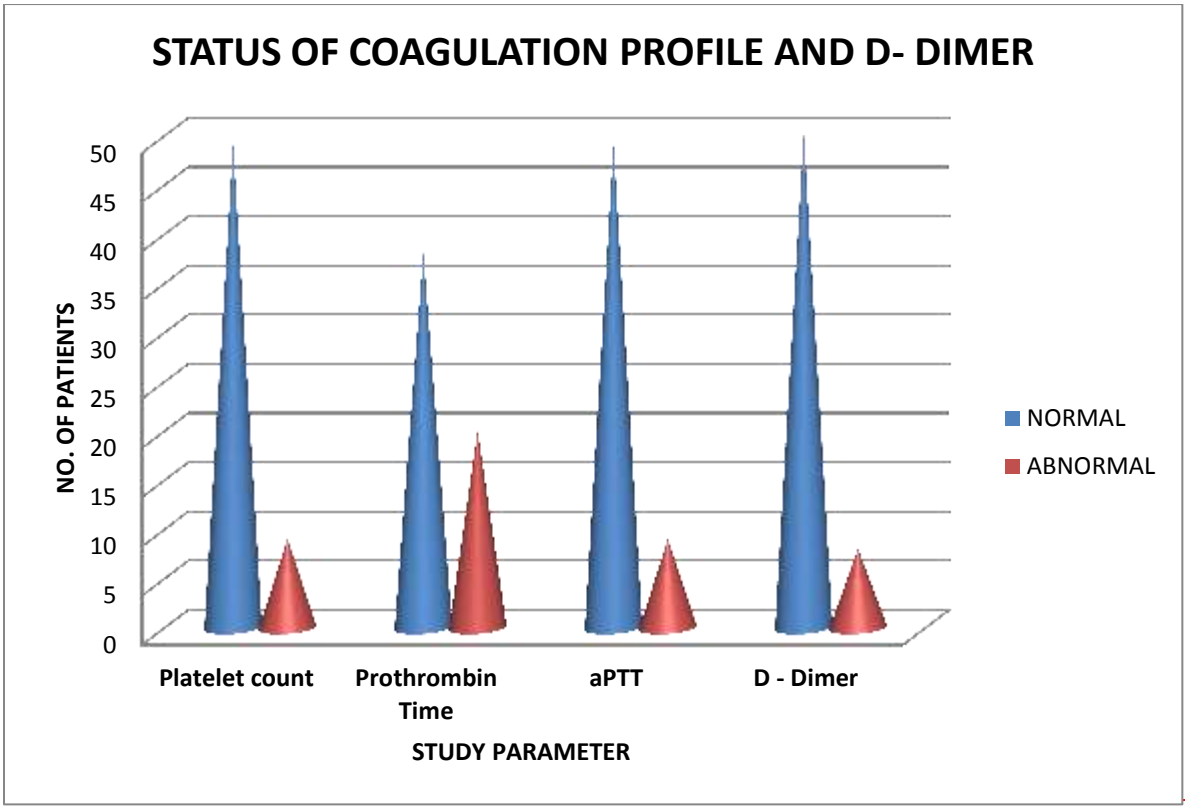


Table 6: Distribution of markers of hyperfibrinolysis and tissue hypoperfusion

Parameters Studied	Normal Results No. of Patients (%)	Abnormal Results No. of Patients (%)	Mean ± SD
MARKERS OF HYPERFIBRINOLYSIS			
Fibrin Degradation Product	52 (89.6%)	6 (10.4%)	-
D – Dimer	50 (86.2%)	8 (13.8%)	-
MARKERS OF TISSUE HYPOPERFUSION			
Base Deficit	49 (84.5%)	9 (15.5 %)	- 2.32 ± 0.33
Serum Lactate	52 (89.6%)	6 (10.4%)	1.29 ± 0.21

6 (10.4%) patients had FDP positive and 8 (13.8 %) patients had D - dimer positive.

Base deficit of -6 mmol/L or greater was observed in 49 patients (84.5%) and elevated serum lactate was observed in 52 patients (89.6%).

Table 7: Univariate analysis showing association of independent variables with Coagulopathy

Independent Variable	Coagulopathy Present No. of Patients (%)	p Value	95 % CI
Gender			
Male (44)	14 (31.8 %)	0.45	0.6 (0.1 - 2.1)
Female (14)	6 (42.8 %)	-	1
Age (Continuous Variable)			
Age		0.27	0.9 (0.9 – 1.021)
Type of Injury			
Blunt Injury (48)	15 (31.2 %)	0.26	2.2 (0.55 - 8.7)
Penetrating Injury (10)	5 (50 %)	-	1
Diabetes Mellitus			
Present (17)	5 (29.4%)	0.7	0.7 (0.21 – 2.4)
Absent (41)	15 (36.6%)	-	1
Hypertension			
Present (13)	6 (46.1%)	0.3	1.8 (0.5 - 6.6)
Absent (45)	14 (31.1%)	-	1

Value of p less than or equal to 0.05 is regarded as significance.

The age when regarded as a continuous variable, there was no significance between the age and presence of coagulopathy.

Among the patients with coagulopathy 14 were male and 6 were female. There was no significant association between the gender and the coagulopathy (p=0.45).Though there were more number of patients with blunt injury having coagulopathy, there was no significant association between type of injury and coagulopathy. (p value = 0.26)

When Diabetes Mellitus and Hypertension was considered, there was no significant association with coagulopathy. p value was found to be 0.7 and 0.3 respectively.

Table 8: Univariate analysis showing association of Tissue hypoperfusion and severity of Injury with coagulopathy

Independent Variable	Coagulopathy Present No. of Patients (%)	p Value	OR (95 % CI)
Tissue hypoperfusion			
Present (9)	7 (%)	0.003**	18.8 (2.72 – 129.73)
Absent (49)	13 (%)		1
Severity of Injury (Continuous Variable)			
Revised Trauma Score	-	0.04*	0.63 (0.4 – 0.9)

Value of p less than or equal to 0.05 is taken as significance. Value of p less than or equal to 0.01 is regarded as highly significant.

Based on the results of base deficit, tissue hypoperfusion was present in 9 patients in total. Among these patients 7 patients (77.7%) had coagulopathy. Thus, tissue hypoperfusion was also significantly associated with the presence of coagulopathy. The p value was found to be statistically significant (p= 0.003)

The mean Revised Trauma Score was 6.57 ± 1.22 among total trauma patients. There was a significant association between the severity of injury and the presence of the coagulopathy with p value of **0.04**.

Table 9 : Univariate analysis showing association between Coagulopathy and blood transfusion

Independent Variable	Blood Transfusion given	p Value	OR (95 % CI)
COAGULOPATHY			
Present (20)	12 (60%)	**0.01***	9.9 (2.72 – 36.25)
Absent (38)	5 (16.6%)		1

* p value of less than or equal to0.05 is regarded as significant. ** p value of less than or equal to 0.01 is regarded as highly significant.

Traumatic coagulopathy was associated with increased blood transfusion requirements and proved to be statistically significant. (p = 0.01)

Table 10: Univariate analysis showing association of Independent variables and Mortality

Independent Variable	Mortality No. of Patients (%)	P Value	OR (95 % CI)
Gender			
Male (44)	4	0.58	0.6 (0.09 – 3.6)
Female (14)	2		1
Age (Continuous variable)			
Age	-	0.49	0.97 (0.9 – 1.05)
Severity of Injury (Continuous Variable)			
RTS		**0.043***	0.13 (0.02 – 0.93)
Coagulopathy			
Present (20)	5 (40.0 %)	**0.027***	12.3 (1.3 – 114.6)
Absent (38)	1 (2.63%)		1
Renal injury			
Present (7)	3 (42.8 %)	**0.01***	12 (1.8 – 80.04)
Absent (51)	3 (5.88 %)		1
Tissue Hypoperfusion (Based on Base Deficit)			
Present (9)	5 (55.5 %)	**0.028***	7.7(1.25 – 46.95)
Absent (49)	1 (2.04 %)		1
Serum Lactate			
Present (6)	4 (66.6%)	**0.01***	12 (1.8 – 80.02)
Absent (52)	2 (3.84%)		1

* p value of less than or equal to 0.05 is regarded as significant. ** p value of less than or equal to 0.01 is regarded as highly significant.

Among the 6 patients who died during the period of follow up, 4 were male and 2 were female. There was no significant association between the gender and the mortality (p valve =0.58). Age when regarded as a continuous variable, there was no significant difference between the age and mortality.

There was a significant association between the severity of injury and mortality with p value of **0.043**. (SD - 0.13 95% CI (0.02 – 0.93))

Mortality was more among the patients with coagulopathy (5 patients (40%)) than patients without coagulopathy (1 patient (2.6%)). The p value was found to be statistically significant (**p= 0.027**) (OR 12.3 95 % CI (1.3 – 114.6))

Based on the ratio of blood urea nitrogen to serum creatinine, in total 7 (12.1%) patients had Renal injury. Among these 7 patients, 3 (42.8 %) died. The association of renal injury and mortality is proved to be significant (**p value = 0.01**)

Out of 9 patients with tissue hypoperfusion, 5 patients (55.5%) died either on the day of trauma or on the second day. The association of tissue hypo perfusion and mortality. The p value was found to be statistically significant (**p= 0.028**)

Serum lactate was found to be abnormal for 6 (10.34%) patients in total. In this, 4 (66.6%) patients died during the period of follow up. The association of serum lactate and mortality was found to be statistically significant (**p= 0.01)**

Table 11: Univariate analysis showing association of Independent parameters of Coagulation Profile and Mortality

Independent Variable	Mortality No. of Patients (%)	P Value	OR (95 % CI)
Platelet Count			
Abnormal (9)	3 (33.3%)	**0.028***	7.6 (1.25 – 46.9)
Normal (49)	3 (6.10%)		1
Prothrombin Time			
Abnormal (20)	5(25.0%)	**0.027***	12.3 (1.3 – 114.6)
Normal (38)	1(2.63%)		1
aPTT			
Abnormal (9)	5(55.5%)	**0.003***	18.8 (2.72 – 129.7)
Normal (49)	1(2.04%)		1
Fibrinogen			
Abnormal (9)	3(33.3%)	**0.028***	7.6 (1.25 – 46.95)
Normal (49)	3(6.12%)		1
Fibrin Degradation Products			
Positive (5)	2(40.0%)	**0.046***	8.16 (1.04 – 64.02)
Negative (52)	4(7.69%)		1
D – Dimer			
Positive (8)	3(37.5%)	**0.017***	9.4(1.48- 59.59)
Negative (50)	3(6.00%)		1

* Value of p less than or equal to 0.05 is regarded as significant. ** Value of p less than or equal to 0.01 is regarded as highly significant.

Out of 9 patients who had abnormal Platelet count 3 patients i.e 33.3 % died during the period of follow up for 14 days. The p value of 0.028 was found to be statistically significant (SD 7.6 95% CI (1.25 – 46.9))

Among 20 patients with elevated PT, 5 patients i.e 25 % died either on day 0 or day 2. The p value was found to 0.027 which was proved to be statistically significant. (SD 12.3 95% CI (1.3 – 114.6))

In 9 patients with elevated aPTT, 5 patients (55.5%) died. There was a significant association between aPTT and mortality with p value of **0.003**. 3 (6%) patients of the total 9 patients with decreased fibrinogen, died. This was also proved to be statistically significant with p value – **0.028**.

2 out of 6 patients with FDP positive died which was significant statistically with **p value of 0.046.** Among 8 patients with D - dimer positive, 3 patients died during the follow up period. This also showed a significant association between D - Dimer levels and mortality. The p value was found to be 0.017.

Table 12: Univariate analysis showing association of Independent variables and length of stay in the hospital

Independent Variable	Length of Stay >= 11 days	p Value	OR (95 % CI)
Tissue hypoperfusion			
Present (4)	3 (75%)	0.47	2.3 (0.22 – 24.07)
Absent (48)	27 (56.5%)		1
Renal injury			
Present (3)	3 (100%)	-	-
Absent (49)	0		1
Coagulopathy			
Present (15)	12 (80 %)	**0.047***	4.22 (1.02 – 17.46)
Absent (37)	18 (48.6%)		1

Analysis done with 52 patients who survived; * Value of p less than or equal to 0.05 is regarded as significant. **p value of less than or equal to 0.01 is regarded as highly significant.

Among 4 patients with tissue hypoperfusion who survived, 3 (75%) patients stayed longer in the ward for >= 11 days than patients without tissue hypoperfusion. The p value was not found to be statistically significant (p = 0.47)

Out of 3 patients with acute renal injury who survived during the follow up period, all the 3 (100%) patients stayed longer in the ward for >= 11 days than patients without renal injury.

Out of 15 patients with coagulopathy who survived during the follow up period, 12 patients stayed in the ward for >= 11 days than patients without

coagulopathy. The p value was found to be statistically significant **(p = 0.047)** and proved that there is association of coagulopathy and length of stay.

Chart 3 : Distribution of various parameters in relation to Morbidity (Length of stay >= 11 days)

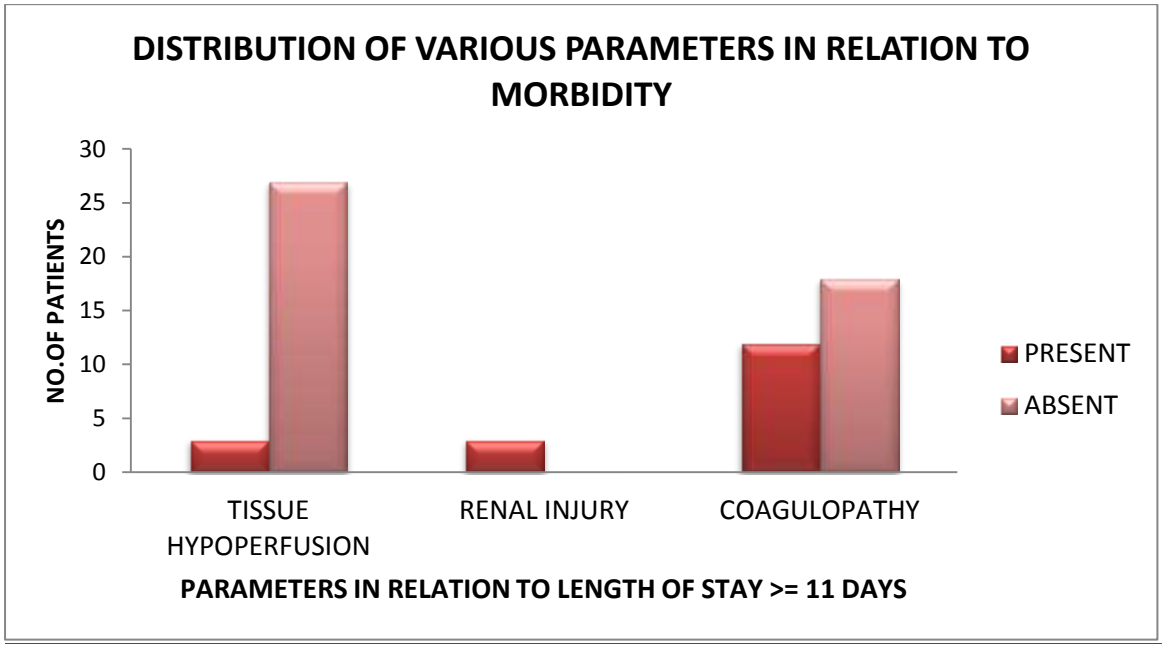


Chart 3 shows the distribution of various other parameters in relation to morbidity. (i.e) length of stay >= 11 days

Table 13: Univariate analysis showing association of Tissue hypoperfusion and Severity of Injury

Independent Variable	Tissue hypoperfusion present	p Value	OR (95 % CI)
RTS (Continuous Variable)	-	0.007**	2.3 (0.22 – 24.07)

*p value of less than or equal to0.05 is regarded as significant. **p value of less than or equal to 0.01 is regarded as highly significant.

Severity of Injury was determined using Revised Trauma Scale. When RTS was regarded as a continuous variable, it was significantly associated with Tissue hypoperfusion. **(p = 0.007)**

Table 14: Univariate analysis showing association of High Lactate level and Severity of Injury

Independent Variable	High Lactate level	p Value	OR (95 % CI)
RTS (Continuous Variable)	-	0.037*	0.34 (0.13 – 0.93)

*p value of less than or equal to 0.05 is regarded as significant. **p value of less than or equal to 0.01 is regarded as highly significant.

The elevated lactate level was also found to be significantly associated with severity of injury**.(p – 0.037)**

Table 15 : Univariate analysis showing association of Presence of Renal Injury and Severity of Injury

Independent Variable	Presence of Renal Injury	p Value	OR (95 % CI)
RTS (Continuous Variable)	-	0.05	0.72 (0.26 – 0.89)

*p value of less than or equal to 0.05 is regarded as significant. **p value of less than or equal to 0.01 is regarded as highly significant.

As the severity of injury increase, the presence of acute renal injury is also more. Thus acute renal injury and severity of injury was also just associated with p value **0.05**

Table 16 : Univariate analysis model showing association of Renal Injury with Coagulopathy

Independent Variable	Coagulopathy No. of Patients (%)	p Value	OR (95% CI)
Renal injury			
Present (7)	4 (57.1 %)	0.19	2.9 (0.53 – 14.58)
Absent (51)	16 (31.3 %)		1

*p value of less than or equal to0.05 is regarded as significant. **p value of less than or equal to0.01 is regarded as highly significant.

Overall 7 patients had acute renal injury. Among these, 4 patients had coagulopathy. Similarly, 16 patients without coagulopathy also presented with acute renal injury. Thus association of acute renal injury and coagulopathy was not statistically significant.(p = 0.19)

Table 17 : Multivariate analysis model showing association of Mortality with other factors

Independent Variable	Mortality No. of Patients (%)	OR (95 % CI)	AOR (95% CI)
Coagulopathy			
Present (20)	5 (40.0 %)	12.3 (1.3 – 114.6)	1.4(0.5- 36.4)
Absent (38)	1 (2.63 %)	1	1
Renal injury			
Present (7)	4 (57.1 %)	32.6 (17.7 – 63.5)	3.2 (0.17 – 56.7)
Absent (51)	2 (3.38 %)	1	1
Tissue Hypoperfusion (Based on Base Deficit) *****			
Present (9)	5 (55.5 %)	7.7(1.25 – 46.95)	23.56(8.4 – 117.12)
Absent (49)	1 (2.04 %)	1	1

*p value of less than or equal to0.05 is regarded as significant.

Multivariate analysis is performed to find the association between different variables like tissue hypoperfusion, coagulopathy and renal injury with mortality. It proved that tissue hypoperfusion is an independent predictor of mortality when compared with other variables.

Table 18 : Multivariate analysis model of Length of stay with other factors

Independent Variable	Length of Stay >= 11 days	OR (95 % CI)	AOR (95% CI)
TISSUE HYPOPERFUSION			
Present (4)	3 (75%)	2.3 (0.22 – 24.07)	1.20(0.096 - 15.11)
Absent (48)	27 (56.5%)	1	1
COAGULOPATHY *			
Present (15)	12 (80 %)	4.22 (1.02 – 17.46)	4.09(1.93 - 17.88)
Absent (37)	18 (48.6%)	1	1

*p value of less than or equal to 0.05 is regarded as significant.

Similarly, multivariate analysis is also performed to find the association between variables like tissue hypoperfusion and coagulopathy with length of stay in hospital (marker of morbidity). It proved that coagulopathy as an independent predictor of morbidity).

Table 19 : Multivariate analysis model of Mortality with various parameters of coagulation profile

Independent Variable	Mortality No. of Patients (%)	OR (95 % CI)	AOR (95% CI)
Activated Partial tissue Thromboplastin Time			
Abnormal (9)	5(55.5%)	18.8 (2.72 – 129.7)	5.7(1.3 – 52.9)
Normal (49)	1(2.04%)	1	1
D – Dimer			
Positive (8)	4(50.0%)	9.4(1.48- 59.59)	23.9(0.45 -85.1)
Negative (50)	2(4.00%)	1	1
Prothrombin Time			
Abnormal (20)	5(25.0%)	12.3 (1.3 – 114.6)	43.6(0.2 – 96.2)
Normal (38)	1(2.63%)	1	1

*p value of less than or equal to 0.05 is regarded as significant.

Among the individual coagulation parameters like PT, aPTT, D - Dimer, aPTT was proved to be an independent predictor of mortality in multivariate logistic regression.

DISCUSSION

Major cause of death and disability worldwide is trauma [119], and in this blood loss accounts for approximately 40% of all trauma deaths. [120]

The prevalence of acute traumatic coagulopathy was found to be 34.5%. This prevalence is much lower when compared to the study done by Erick Mujuni et al in Uganda population which was 54%.[112] Other studies reported the prevalence ranging from 24 to 34% which is represented in table 20. This could be due to the small sample size which includes both minor and major cases of trauma.

Table 20: Prevalence of Coagulopathy mentioned by other studies.

Study done by	No. of Patients	Prevalence of Coagulopathy
Brohi K et al 2003 [95]	1088	24%
Macleod at al 2003 [8]	10790	28%
Meagle et al 2007 [14]	8724	34%
Brohi.K et al 2007 [6]	208	10%

TYPE OF INJURY

Coagulopathy was reported more commonly with blunt injury than penetrating injury but it was not statistically significant. This finding was similar to the report mentioned in a study done by Erick Mujuni et al in Uganda population.[112] and in a study by Johansson et al.[110]. No other studies reported the relationship between the type of injury and occurrence of coagulopathy.

SEVERITY OF INJURY

As the injury severity increases, the occurrence of coagulopathy also increases in our study with p value of 0.027. This was as same as proved by other studies by Cosgriff et al and Brohi K et al [92, 93]

ACUTE RENAL INJURY

Acute renal injury occurs generally in hospitalized patients and carries a high mortality [121-123]. The causes are as follows:

- Pre-Renal
- Intrarenal and
- Post-Renal. [124-126]

Pre-renal failure is a reversible increase in serum creatinine and urea due to decreased renal perfusion, which in turn leads to decreased GFR [126]

When the blood urea concentration is raised, measurement of the serum creatinine concentration will definitely differentiate glomerular failure from prerenal uraemia. [127-128]

Hemorrhage increases the risk of acute renal injury or multiple organ failure and late mortality [120.]

There were 7 patients with acute Renal Injury in total (12.1%) and 4 patients (57.1%) had coagulopathy. This was reported as 25.3% in coagulopathy patients and 8.4 % in patients without coagulopathy in a study by Erick Mujini et al.[112] and other studies by Brohi.K et al.[6]

TISSUE HYPOPERFUSION

Base Deficit & Lactate:

Previous studies have shown that Base deficit cannot be used as a substitute for serum lactate. [129 -130] Base Deficit had been proven to be impervious for detecting elevated lactate. [131] Mikulaschek et al proved that decisions regarding resuscitation would have been wrong 33-58% of the time if Base deficit had been used as the only criterion. [132]

Another study reported that the lactate level is a distinct interpreter and may not essentially corresponding base deficit.[133]

Similarly, in this study we did not correlate base deficit and arterial lactate. But elevated levels of arterial lactate were significantly associated with mortality with p value of 0.001.

The base deficit is correlated with injury severity and degree of blood loss in previous studies. [46-50] In the same way, there was a significant association with severity of injury and base deficit of -6 mmol / L. Here it is mentioned as tissue hypoperfusion.

Base deficit of –6 mmol/L was found to be an indicator of severe injury, prolonged stay in hospitals, and associated with increased requirement of blood transfusion.[134] The association of tissue hypoperfusion with severity of injury was proved to be significant as established by other studies. Tissue hypoperfusion as an indicator of increased length of stay was disproved in this study. (no significant association between tissue hypoperfusion and length of stay). This can be due to correction of hypoperfusion due to blood transfusion than other parameters that

determine the outcome. But the correlation of tissue hypoperfusion and transfusion requirements is not done as there is no standard protocol adopted for blood transfusion.

CLINICAL OUTCOME

Mortality

Severe bleeding is one of the chief reasons of mortality [135] during first 48 hours in major trauma. [136]

The overall Mortality was 6 patients (10 %), This is lower mortality than a study conducted by Kirya at Mulago hospital where the mortality was 26%.[137]

On the whole, the rate of mortality ranges from 15% to 20% represented in Table 21, however these studies were undertaken by trauma care centres with great resources.

Table 21 : Percentage of Mortality as reported by other studies.

Study done by	No. of Patients studied	Mortality in patients with Coagulopathy	Overall Mortality
Brohi K et al 2003 [95]	1088	46%	11%
Macleod at al 2003 [8]	10790	19%	6%
Meagle et al 2007 [14]	8724	28%	8%
Brohi.K et al 2007 [6]	208	62%	8%

Patients who arrive in the emergency department with a coagulopathy are three to four times more likely to die [6,8,93,11] and eight times more likely to die within the first 24 hours. [94]

The mortality was more in patients with coagulopathy (i.e) 5 patients (40%) than in patients without coagulopathy 1 patient (2.6 %) **(p value = 0.027)**. This was reported as 29.3 % in coagulopathic and 12.2% in non coagulopathic group in a study by Erick mujini et al.[112] This was also more when compared to other studies mentioned in Table 19, which may be due small sample size.

Coagulopathy can be used as an independent predictor of death said by Brohi K et al. [93]

This study also proved that tissue hypoperfusion was a good predictor of mortality in trauma patients among other parameters like coagulopathy and renal injury. This finding disproved the conclusion from a study by Erick Mujini et al [112.] Erick Mujini et al concluded that coagulopathy as an independent predictor of mortality. The possible explanation could be due to small sample size and very less number of patients with tissue hypoperfusion compared to patients with coagulopathy.

Among tissue hypoperfusion and coagulopathy, coagulopathy was found to be a strong predictor of morbidity which was studied using longer length of stay either in ICU or in general ward. This was also reliable with a study by Brohi.K et al [95]

Length of stay

Patients who survived are 52 (90%) in number. They were taken for analysis of Length of Stay in hospital. Overall mortality of 10% i.e 6 patients died. In this study there was a significant association between length of stay which was regarded

as morbidity parameter and coagulopathy (p value = 0.043). This is consistent with other studies [6, 8, 93, 11] and similar to Brohi. K et al study report which states that Coagulopathy present during admission is associated with prolonged hospital stays.[6]

BLOOD TRANSFUSION

It is very vital to identify the need of blood transfusion early because it has been shown that a postponement in the commencement of coagulation therapy is associated with worse clinical outcome.[138 -139] There is an evidence that the use of high plasma : RBC ratios in patients can increase complication rates. [140 -141]

But here in our study there was no strong association between blood transfusion requirements and coagulopathy. A total of 12 patients (60%) with coagulopathy were transfused and 5 patients (13.15%) were transfused with blood products even in the absence of coagulopathy (p =0.001). This could probably due to bleeding at the site of accident and continuous loss secondary to coagulopathy. The transfusion requirement for those without coagulopathy may be due failure to follow standard protocol for blood transfusion in our hospital setup.

COAGULATION TESTS:

Routine coagulation tests, such as PT, aPTT are used to assess coagulopathy and to guide therapy.[93] The value of these standard coagulation tests in effectively reporting the intricacies of trauma-associated coagulopathy has been challenged.[93, 142-143]

Platelet Count:

Canine studies had shown that sequestration of platelets in the liver and spleen contributes to bleeding induced by hypothermia.[144-145] Rewarming quickly reversed sequestration. Effects of hypothermia on platelet function was proven by studies conducted in other species.[146 -147] Hypothermia as already explained, very common in patients with trauma.

In trauma, previous clinical studies have demonstrated attenuation of platelet stimulation to ADP agonism for patients in hemorrhagic shock, [148] and after head injury,[149] with the diminished platelet response to ADP more prominent in patients who died than patients who survived after life-threatening injury.[150]

Hence abnormal platelet count was significantly associated with mortality with p value of 0.028. Out of 9 patients with abnormal platelet count, 3 patients died during the follow up period.

Prothrombin Time :

Quick and precise determination of prothrombin time may help in faster control of bleeding induced by coagulopathy.[151] Among 20 patients with abnormal prothrombin time, 15 patients survived and 5 patients (25%) died. Thus Prothrombin time can be used to assess the coagulation status as well as to predict mortality.(p value 0.027)

Thus from this study, we found that prothrombin time should be done for all trauma patients in order to detect early coagulopathy changes.

aPTT :

aPTT can be prolonged in the presence of hypothermia. In a study, long-lasting acidosis for more than 150 min can result in prolongation of the aPTT and decreases

in factor V level. [152] As hypothermia and acidosis both are common in patients with trauma, aPTT should also be evaluated in trauma.

Among 20 patients with coagulopathy, 9 patients alone had prolonged aPTT. Univariate analysis showed prolonged aPTT is significantly associated with mortality with p value of 0.003. This finding was consistent with other studies [112.]

Macleod et al also reported that reported that the PT and aPTT can be used as independent predictors of mortality whereas platelet count cannot be used.[8]

Fibrinogen level :

In a recent study, hypotension, increased base deficit and increased degree of injury (ISS $\geq$ 25), were associated with decreased fibrinogen levels.[153] Fibrinogen exhaustion is associated with poor outcomes.[154] This was also proved by in this study that decreased fibrinogen level was associated with significant mortality (p value – 0.028)

MARKERS OF FIBRINOLYSIS :

Fibrinolysis clears thrombi from the vasculature and limits the formation of thrombus. Hence enormous activation of coagulation due to injuries may lead to unrestrained stimulation of the fibrinolytic system with further creation of antithrombin.[155]

Hypercoagulable state in trauma patients has been proved by many studies [156 - 158] These patients are prone to thromboembolic complications. [159] Coagulopathy on admission is a risk factor of venous thromboembolism in trauma patients. [160]

Laboratory evidence has established both decreased fibrinolytic and increased fibrinolysis in trauma patients.[161 - 163] Increased fibrinolytic activity was found immediately following trauma and after 24 h in patients with mild to moderate injury it returns to normal. In major injuries it remains elevated.[164] Fibrinolytic activity is increased in the presence of hypothermia was also proved by a study.[165]

Early fibrinolysis was reported in 34% of trauma patients and associated with increased blood transfusion requirements, coagulopathy, and bleeding- related death.[166]

Hyperfibrinolysis was associated with increased mortality and appears to be related to the injury severity in trauma.[35]

6 patients had positive FDP results in this study. Among those patients, 2 patients (40%) died. Thus FDP was also significantly associated with mortality (p value – 0.046). This was also the same as proved other study done by Fei et al [114] Fei et al reported that FDP is the best independent indicator of mortality in ICU patients.

In this study, when fibrinolysis was considered by positive D – dimer levels, 8 patients (13.8%) had fibrinolysis and 3 patients (3 %) died during the follow up period. D- Dimer level was also significantly associated with mortality. (p value 0.017)

Thus hyperfibrinolysis was associated with high mortality rates, it can be used as a predictor of poor outcome as proved by other studies. [114]

CONCLUSION

India is a developing country with a more number of trauma deaths and it is one of the leading causes of death. Yet there has not been a major advancement in trauma research and coagulation studies in our country.

The association of coagulopathies with trauma has been well established, yet it still faces criticism from various sects of medicine. There is a need for more evidence-based studies in this field as the concepts of trauma resuscitation are undergoing changes.

Patients presenting with an established coagulopathy were likely to have poor outcomes, and must be identified as soon as possible and treated aggressively.

Severe injury itself, can lead traumatic coagulopathy which is the major cause of failure of hemostasis in these patients. Instantaneous control of blood loss, aggressive resuscitation and quick correction of hypothermia improves the survival rate of these patients.

In the quest to improve severe trauma outcomes in an environment with limited resources, assessment of coagulation by means of coagulation profile should be done routinely. In addition, inexpensive and operational ways to assess or to prevent coagulopathy in early stages of trauma should be investigated further.

LIMITATIONS

- Small sample size
- As the Prothrombin time varies for different laboratories, PT –INR should have been considered.
- In blood transfusion, blood components and number of units transfused was not taken into consideration.
- Core Temperature was not measured as it can indicate hypothermia- an aetiology of coagulopathy.
- Amount of IV fluids administered during resuscitation and during stay in the hospital was not taken into account.

RECOMMENDATIONS

- This study can be extended by including a large number of trauma patients
- Parameters like Protein C, Thrombomodulin, Anti-thrombin can be included to study the mechanism of traumatic coagulopathy.
- Thromboelastography (TEG) can be used instead of routine coagulation tests. TEG examines whole blood coagulation and provides information on the rate of clot formation. These are key elements in determining the likelihood of platelet and clotting factor deficiencies, and fibrinolysis.

PROFORMA

1. Name of the Patient : IP.No :
2. Age :
3. Sex :
4. Occupation :
5. Educational status :
6. Date and Time of Admission :
7. Present Illness :
8. **History of Present illness** :
    - Time & Date of Accident :
    - Cause of Injury :
    - Type of Injury :
    - H/o first aid :
    - Drugs given during first aid : IV fluids / Blood transfusion
9. **Past Medical History** :
    - H/s/o Diabetes Mellitus : Yes / No
    - H/s/o Hypertension : Yes / No
    - H/s/o Chronic Renal Failure : Yes / No
    - H/s/o Liver Disease : Yes / No
    - H/s/o Heart disease : Yes / No
10. **Past Surgical History**
    - H/o valve replacement surgeries

11. Drug History

12. Menstrual History

EXAMINATION

- **General Examination**
  - Pallor / Icterus / Pedal edema
- **Vital signs**
  - Temperature -
  - Pulse rate -
  - Blood Pressure -
  - Respiratory Rate -
- **Systemic Examination**
  - CVS -
  - RS -
  - Abdomen -
  - CNS (GCS Scoring) -
- **Grading of Injury**

  Revised Trauma Score -
- **Length of stay**
- **Blood transfusion given or not**

PARAMETERS

S.No	PARAMETERS	DAY 0	DAY 2	DAY 6	DAY 14
1.	Temperature				
2.	Pulse Rate				
3.	Respiratory Rate				
4.	Blood Pressure				
5.	Blood Urea (mg/dl)				
6.	Serum Creatinine (mg/dl)				
7.	Bleeding Time (mins)				
8.	Clotting Time (mins)				
9.	Platelet count (lakhs / cu.mm)				
10.	Prothrombin Time (sec)				
11.	Activated Tissue Thromboplastin Time (sec)				
12.	Fibrinogen (mg/ dl)				
13.	Fibrinogen Degradation Product (+ / -)				
14.	D – Dimer (+ / -)				
15.	Base Deficit (ABG Report)				
16.	Serum Lactate				

CONSENT FORM

(To be obtained from subject)

You are requested to participate in a study conducted in department of Physiology titled **"Pattern of Coagulation profile in patients with Trauma"**

Your participation in this study is voluntary. You act at liberty to participate withdraw from the study. Please read this consent form carefully and ask the Consultant, any questions you may have about the study before signing.

EXPLANATION OF PROCEDURES:

If you agree to participate in this study, we will ask some questions to you and collect relevant information you may be examined by the investigator if found to have illness. Data from the study will be used for research purpose only. The results of the study will not be given to you directly. There will be no cost to you for participating in this study. The venous blood sample 3 ml will be screened for parameters like Bleeding Time (BT), Clotting Time (CT), Prothrombin Time (PT), activated Partial Tissue Thromboplastin Time (aPTT), Platelet counts, Fibrinogen, Fibrinogen Degradation Product, D-dimer, Blood Urea, Serum Creatinine and Serum Lactate. 2ml of arterial blood will be taken for Arterial Blood Gas (ABG) analysis

POTENTIAL BENEFITS:

Your participation will help us to study the incidence and probable cause of this problem and the results of this study will be beneficial for future generations.

ASSURANCE OF CONFIDENTIALITY:

The information concerning your participation in the study will be kept confidential to the full extent permitted by law and used only for scientific purpose. No one except members of the research team will have access to the results. Your name will not be disclosed in any report or released in any way.

PATIENT CONSENT:

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I have not received money from participants in this study.

Signature of Subject Signature of Witness

Date:

Signature of Researcher

(Dr.B.AANANTHA LAKSHMI)

REVISED TRAUMA SCORE CALCULATION

Revised Trauma Score - Table 1

Systolic BP	Respiratory Rate				
	+ 30	29 - 10	9 - 6	5 - 1	0
> 90	A1	B1	C1	D1	E1
89 -76	A2	B2	C2	D2	E2
75 - 50	A3	B3	C3	D3	E3
49 - 1	A4	B4	C4	D4	E4
0	A5	B5	C5	D5	E5

(Carry Alphanumeric Value from Table 1 to RTS - Table 2)

Revised Trauma Score - Table 2

TABLE 1 VALUE	Glascow Coma Scale				
	15 - 13	12 - 9	8 - 6	5 - 4	3
A1	7.6	6.6	5.7	4.7	3.8
A2	6.8	5.9	4.9	4.0	3.1
A3	6.1	5.1	4.2	3.3	2.3
A4	5.4	4.4	3.5	2.5	1.6
A5	4.6	3.7	2.7	1.8	0.9
B1	7.8	6.9	6.0	5.0	4.1
B2	7.1	6.2	5.2	4.3	3.4
B3	6.4	5.4	4.5	3.6	2.6
B4	5.6	4.7	3.8	2.8	1.9
B5	4.9	4.0	3.0	2.1	1.2
C1	7.3	6.3	5.4	4.4	3.5
C2	6.5	5.6	4.7	3.7	2.8
C3	5.8	4.9	3.9	3.0	2.0
C4	5.1	4.1	3.2	2.3	1.3
C5	4.3	3.4	2.5	1.5	0.6
D1	7.0	6.0	5.1	4.2	3.2
D2	6.2	5.3	4.4	3.4	2.5
D3	5.5	4.6	3.6	2.7	1.8
D4	4.8	3.8	2.9	2.0	1.0
D5	4.0	3.1	2.2	1.2	0.3
E1	6.7	5.7	4.8	3.9	2.9
E2	5.9	5.0	4.1	3.1	2.2
E3	5.2	4.3	3.3	2.4	1.5
E4	4.5	3.5	2.6	1.7	0.7
E5	3.7	2.8	1.9	0.9	0.0

Revised Trauma Score is a physiological scoring system, with high inter-rater reliability and demonstrated curacy in predicting death. It is scored from the first set of data obtained on the patient, and consists of Systolic Blood Pressure, Respiratory Rate and Glasgow Coma Scale.

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